The Adrenal Cortex and B-Vitamins in Diabetic Retinopathy

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The classic work of MacKenzie and Nettleship[1] in 1877 first demonstrated capillary microaneurysms in the retina of a diabetic patient at autopsy. This important discovery was soon forgotten, and knowledge about diabetic retinopathy entered a dark age in which it was confused with other disease processes. The renaissance in 1943 can be attributed to the rediscovery of retinal capillary aneurysms by Ballantyne and Loewenstein.[2]

The application of newer staining[3] and injection[4] technics to flat preparations of whole retinas has permitted visualization of the entire retinal vascular tree. When these methods were applied to diabetic retinas, diabetic retinopathy emerged as a distinct pathologic entity. Retinas from patients with typical diabetic retinopathy exhibit as the basic pathologic change enormous numbers of discrete saccular aneurysmal dilatations of capillaries. Some of the aneurysms are thin-walled, but most are enclosed in thickened laminated layers of hyaline. Clusters of aneurysms, which tend to appear episodically in crops, account for the persistent petechiae which characterize the ophthalmoscopic picture of the disease. Leakage of proteins and red cells through the walls of the aneurysms explains many of the surrounding exudates and hemorrhages. Although capillary aneurysms are found in venous occlusion,[5] malignant hypertension,[6] pernicious anemia,[7] chorioretinitis,[8] and in some normal retinas,[8] those characterizing diabetic retinopathy are unique in pattern, number and location.

At autopsy hyalinized nodules are frequently found in the glomeruli of diabetic kidneys as first described by Kimmelstiel and Wilson.[9] That these renal lesions occur exclusively in diabetics with retinopathy was demonstrated independently by Ashton[10] and Friedenwald[11] (Table 1). In the two series of diabetics combined, Kimmelstiel-Wilson lesions were present in 32 of the 55 cases of diabetic retinopathy studied histologically. There was no instance of Kimmelstiel-Wilson nodules in any of the 42 diabetic patients in whom flat preparations of retinas revealed no aneurysms. Furthermore, aneurysmal dilatations of capillaries were seen in the affected glomeruli, and no difference could be demonstrated histochemically in the staining characteristics of the nodules in the kidneys and the hyalinized capillary aneurysms in the retinas.[10,12] The retinal and renal lesions must therefore be considered as manifestations of the same vascular disease process. Since the larger capillary aneurysm can be readily seen and studied ophthalmoscopically, a particularly valuable approach is available for the early identification of this group of diabetic patients, as well as for the evaluation of their course and the results of various therapeutic efforts.

THE ROLE OF ADRENAL CORTEX IN DIABETIC RETINOPATHY

Recent investigations have accumulated considerable clinical, therapeutic, histopathologic, and experimental evidence that the adrenal cortex may be implicated in the pathogenesis of diabetic retinopathy and the Kimmelstiel-Wilson kidney lesion.[13] In some diabetics without retinopathy there appears to be an actual decrease in certain adrenocortical capacities, whereas those diabetics with retinopathy exhibit evidence of excessive adrenocortical function. Attempts to verify this hypothe-

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TABLE 1
Incidence of Kimmelstiel-Wilson kidney lesions in patients with diabetes

	Friedenwald[11] (1950)	Ashton[10] (1949)	Total
With retinopathy	25 of 43 (58%)	7 of 12 (58%)	32 of 55 (58%)
Without retinopathy	0 of 33	0 of 9	0 of 42

sis have been greatly hampered by the lack of direct methods of measuring adrenocortical function and by the inadequacies of current clinical methods of evaluating the status of the adrenal cortex. It must therefore be emphasized that the evidence to support this thesis can only be suggestive and not conclusive. However, all studies and analyses have been entirely consistent with a role of a relative excess of certain functions of the adrenal cortex in the pathogenesis of diabetic retinopathy. It is the purpose of this paper to review the evidence for such a hypothesis.

Clinical Evidence

Clinical observations indicate that excessive activity of the adrenal cortex is related to the onset and progression of diabetic retinopathy and the Kimmelstiel-Wilson syndrome. Thus, diabetic retinopathy has been noted to appear for the first time in nonhypertensive diabetics during pregnancy and to clear completely following delivery.[13,14] In addition, many diabetics with retinopathy have been observed whose ocular disease showed startling progression during the last trimester of pregnancy and subsequent regression postpartum.[15] On the other hand, the pregnant state is associated with other metabolic and endocrine changes in addition to the increase in adrenocortical activity.

Retinal capillary aneurysms have been observed clinically to appear in nondiabetic patients during intravenous corticotropin therapy and to disappear following cessation of treatment.[16] Rifkin and co-workers[17] have noted an increase of urinary signs of diabetic glomerulosclerosis following the administration of corticotropin.

Since infections and acidosis stimulate the adrenal cortex,[18–20] the statistical clinical reports of poor control as a factor in the development of diabetic retinopathy and nephropathy[21–23] are consistent with the thesis of a role of adrenocortical hyperfunction in this group of diabetic patients.

Diabetics with retinopathy excrete variable but excessive amounts of free oxysteroids in the urines.[24–26] In some cases these have been noted both by the phosphomolybdate-reducing method and by the Porter-Silber technic. Such increased excretion is extremely indicative of excessive secretory activity of the zona fasciculata of the adrenal cortex. A large part of the urinary oxysteroids excreted by this group of diabetics appears to be closely related to compound F.[26] Diabetic patients without retinopathy, on the other hand, excrete much smaller amounts of oxysteroids in their urines. Miller and Mason[27] reported that 17-ketosteroid excretion was decreased in diabetics without complications. Decreased ketosteroid excretion has been similarly reported in alloxan-diabetic rabbits.[28]

The fall of circulating eosinophils following the administration of corticotropin has been proposed by Thorn[29] as an index of activity of the adrenal cortex. Unfortunately, this test is subject to all the uncertainties involved in the large variety of factors influencing eosinophil levels. The method also does not distinguish between normal and hypernormal function of the adrenal cortex. However, the test does provide at least a qualitative indication of reduced capacity of the adrenal cortex.

Soon after the Thorn test was devised, it was reported that some diabetic patients failed to obtain the normal eosinopenia of at least 50 per cent four hours after the intramuscular administration of 25 U.S.P. units of corticotropin.[30] Furthermore, some diabetic individuals did not demonstrate a normal decrease in circulating eosinophils after surgery.[31] It has been clearly established since that time, that this failure to respond was exhibited primarily by diabetics free of retinopathy.[13] Almost all diabetics with retinopathy showed a prompt eosinopenia after corticotropin; that is, their adrenals were responsive to this hormone. However, approximately one-half of diabetics with no evidence of retinopathy failed to give a normal eosinopenic response to corticotropin, resembling patients with Addison's disease or bilateral adrenalectomy (Table 2). The lack of response to corti-

TABLE 2
Eosinopenic response to corticotropin by diabetics

	No. of Patients	Normal Response*	Subnormal Response
With retinopathy	26	24 (92%)	2 (8%)
Without retinopathy	67	34 (51%)	33 (49%)

* A fall in circulating eosinophils of 50% or more 4 hours after the administration of 25 U.S.P. units of corticotropin was considered a normal response.

cotropin by these diabetics without retinopathy could be due to an adrenocortical defect or to an abnormality of eosinophil response. Their prompt eosinopenic response to 100 mg. of cortisone is suggestive evidence for the former mechanism, but this cannot be considered as proved.

Additional clinical evidence for a relatively decreased functional capacity of the adrenal cortex in the diabetic without retinopathy is revealed by the reported greater insulin sensitivity of this group as compared with the retinopathic diabetic.[32] However, such differences in responsiveness to insulin have not been noted by other observers.

Therapeutic Evidence

There are also therapeutic reports which tend to confirm the hypothesis of a contributing role of the adrenal cortex in the progression of this entity. These are based on the improvement in diabetic retinopathy following a decrease of adrenocortical function. Thus, Green[33] reported improvement in a case of diabetic and hypertensive retinopathy following bilateral adrenalectomies. Poulsen[34] reported the case history of a diabetic woman with extensive retinopathy, which cleared completely following the development of postpartum Simmonds' disease with panhypopituitarism. Olivecrona[35] has noted arrest of this disease process following hypophysectomy.

It is well known from the work of Albright,[36] Greep and Jones,[37] and Venning and Browne[38] that testosterone decreases the production of corticotropin both in animals and in man. Thus, Greep and Jones have shown that testosterone produces atrophy of the hypophysis and subsequent marked lipoid depletion and atrophy of the zona fasciculata of the adrenal cortex in rats. Furthermore, testosterone decreases oxysteroid excretion in normal patients,[38] in Cushing's syndrome,[36] and in diabetics with retinopathy.[25] It also decreases the eosinophil response to epinephrine in some patients.[39] It frequently increases the sensitivity of the diabetic to insulin and decreases his insulin requirements,[40] thus simulating adrenalectomy. Testosterone administration has been noted to improve cases of Cushing's syndrome.[41] There are reported[42] early beneficial effects in some patients with diabetic retinopathy, but other observers[40,43] failed to note improvement of retinopathy following testosterone.

In respect to these disagreements as to the therapeutic effects of testosterone, it is important to point out that diabetic retinopathy in its early stages is a fluctuating disease with periodic exacerbations and remissions. Long-continued observations are therefore required to evaluate therapy. On the other hand, it is possible that patients receiving long-continued testosterone injections may become resistant to the influence of this hormone in suppressing adrenocortical activity. Our own experience was that some patients with retinopathy showed an increased insulin sensitivity at the onset of testosterone therapy, but that this increased sensitivity diminished after some months of continued testosterone administration. The course of the disease was not altered in these patients.

Histopathologic Evidence

Histopathologic observations by Rich[44] have disclosed typical Kimmelstiel-Wilson renal lesions in one proved nondiabetic patient following prolonged corticotropin therapy. At autopsy, the adrenals of diabetic individuals with these lesions weigh more on the average, display more lipoid vacuolization, and have a higher incidence of cortical adenomas than do the adrenals of diabetics without such nodular lesions in the glomeruli of their kidneys. In Table 3 are presented the available weights of the adrenals of 45 consecutive diabetics in the autopsy files of the Johns Hopkins Hospital correlated with the presence or absence of Kimmelstiel-Wilson lesions. In the Kimmelstiel-Wilson group, the adrenals averaged 24 per cent heavier than the adrenals of diabetics without this type of renal involvement.[13] When the adrenals of 155 diabetics and 91 nondiabetics were divided histologically into two groups on the basis of lipoid vacuolization of the zona fasciculata, a remarkable difference was noted between the two groups of diabetic patients (Table 4). Thus, whereas 86 per cent of diabetics with glomerulosclerosis had vacuolated adrenals, only 12 per cent of diabetics without nephropathy fell into this classification. It was also demonstrated that this difference could not be explained on the basis of cause of death (Table 5).[13] Although diabetic patients without nephropathy have a higher incidence of acidosis before death and the Kimmelstiel-Wilson group have more uremia, these findings also do not appear to explain the correlation of lipoid vacuolization of the zona fasciculata with the specific renal lesions. Thus, among 56 diabetics (30 with Kimmelstiel-Wilson lesions and 26 with other types of kidney disease) dying with repeatedly elevated blood nonprotein nitrogen values, 29 of the 30 patients with Kimmelstiel-Wilson lesions had vacuolated adrenal cortices, whereas only 1 of the 26 whose kidney disease was not of the Kimmelstiel-Wilson type had similar vacuolization (Table 6-A).[45] In the 24 diabetics without glomerulosclerosis who died in acidosis, only 3 had vacuolated adrenal cortices. Although only 7 Kimmelstiel-Wilson diabetics died in acidosis, the adrenal cortex was vacuolated in all but one (Table 6-B).

Russi[46] reported an incidence of adenomas of the adrenal cortex of 1.45 per cent in a series of 9000 consecutive autopsies (Table 7). Among the 270 diabetics in this series, however, adenomas occurred in 8 per cent. In reviewing the records of the diabetics and nondiabetics used for their vacuolization study, Becker and Friedenwald[45] noted adrenocortical adenomas in 2 of the 91 nondiabetics and in 12 of the 155 diabetics. The findings in this small series were thus in good agreement with the much larger series of Russi. When the 155 diabetics were divided on the basis of presence or absence of Kimmelstiel-Wilson renal lesions, in only 3 of the 91 nonnephropathic diabetics were adenomas of the adrenal cortex recorded, whereas the incidence in the glomerulosclerosis group was 9 of 64 (14 per cent).

TABLE 3
Weight of adrenals in diabetics[13]

	No. of cases	Average weight of adrenals
With Kimmelstiel-Wilson lesions	22	20.7 gm.
Without Kimmelstiel-Wilson lesions	23	16.7 gm.

TABLE 4
Lipoid vacuolization of zona fasciculata of adrenal cortex[13]

	No. of Patients	Vacuolization	No Vacuolization	Unclassified
Diabetics:				
Without Kimmelstiel-Wilson lesions	91	11 (12%)	76 (84%)	4 (4%)
With Kimmelstiel-Wilson lesions	64	55 (86%)	3 (5%)	6 (9%)
Nondiabetics	91	68 (75%)	16 (17%)	7 (8%)

TABLE 5
Relation of vacuolization of zona fasciculata to cause of death in classified diabetics and nondiabetics[13]

Cause of Death	Diabetics without Kimmelstiel-Wilson lesions		Diabetics with Kimmelstiel-Wilson lesions		Nondiabetics	
	Vacuolated	Nonvacuolated	Vacuolated	Nonvacuolated	Vacuolated	Nonvacuolated
I	1 (4%)	25 (96%)	15 (88%)	2 (12%)	6 (35%)	11 (65%)
II	5 (11%)	39 (89%)	24 (96%)	1 (4%)	45 (90%)	5 (10%)
III	5 (29%)	12 (71%)	16(100%)	0 (0%)	17(100%)	0 (0%)

I = Severe burns, traumatic shock or hemorrhage, or severe infection (septicemia, peritonitis, meningitis, etc.).
II = Chronic debilitating disease, carcinoma, or chronic infection.
III = Cardiorenal disorders or sudden accident.

TABLE 6
Vacuolization of zona fasciculata[45]

A. In Patients Dying in Uremia*

	No. of Patients	Vacuolated	Nonvacuolated
Diabetics:			
Without Kimmelstiel-Wilson lesions	26	1 (4%)	25 (96%)
With Kimmelstiel-Wilson lesions	30	29 (97%)	1 (3%)
Nondiabetics	50	42 (84%)	8 (16%)

B. In Diabetic Patients Dying in Acidosis

	No. of Patients	Vacuolated	Nonvacuolated
Without Kimmelstiel-Wilson lesions	24	3 (12.5%)	21 (87.5%)
With Kimmelstiel-Wilson lesions	7	6 (86%)	1 (14%)

* Blood NPN over 60 mg. per 100 cc.

TABLE 7
Incidence of adrenocortical adenomas

	Unselected Cases	Diabetics
Russi[46] (1945)	131 of 9000 (1.45%)	21 of 270 (8%)
Becker & Friedenwald[45] (1952)	2 of 91 (2%)	12 of 155 (8%)
With Kimmelstiel-Wilson lesions		9 of 64 (14%)
Without Kimmelstiel-Wilson lesions		3 of 91 (3%)

TABLE 8
Incidence of cortisone-induced renal lesions in rabbits[13]

	No. of Rabbits	No. with Lesions
Cortisone*	29	9 (30%)
Cortisone + Alloxan	16	12 (75%)
ACTH†	10	0
ACTH + Alloxan‡	10	4 (40%)
Alloxan‡	10	0

* 4 mg./kg./day for 21 days.
† 10 mg./kg./day for 21 days.
‡ 200 mg./kg. intravenously.

Experimental Evidence

Extremely important evidence for implicating the adrenal cortex in the pathogenesis of diabetic retinopathy stems from work with experimental animals. Lukens and Dohan[47] reported glomerular lesions simulating those described by Kimmelstiel and Wilson in the kidneys of a dog made diabetic for five years by injections of anterior pituitary extracts. Rich[48] noted that glomerular nodules resembling the Kimmelstiel-Wilson renal lesions appeared in normal rabbits following the daily administration of cortisone for three weeks. Becker[13] demonstrated that when alloxan-diabetic rabbits were similarly injected with cortisone* the incidence of renal lesions induced was increased from 30 per cent in the nondiabetic to 75 per cent in the alloxanized rabbits (Table 8). In addition, a few of the diabetic animals developed what appeared to be retinal capillary aneurysms. Alloxan diabetes alone failed to produce renal lesions in rabbits. This is perhaps not surprising, for these animals demonstrate decreased adrenocortical activity as measured by steroid excretion.[28] In agreement with the findings of Rich, no lesions were seen in normal rabbits injected with corticotropin.† However, when alloxan-diabetic animals were subjected to the repeated administration of corticotropin, lesions appeared in their kidneys (Table 8). Thus, a means is available for the experimental production of both the renal and ocular lesions. Furthermore, it would appear that the diabetic state and hyperfunction of the adrenal cortex contribute to the pathogenesis of the lesions of diabetic retinopathy and nephropathy.

THE INTERRELATIONSHIPS OF B-VITAMINS, ADRENOCORTICAL FUNCTION AND DIABETES

Recently attempts have been made to approach the problem from the nutritional and enzymatic points of view in order to learn the more intimate details of this metabolic disorder. As early as 1896, Gilbert and Carnot[49] reported that the administration of liver often had a beneficial effect in diabetes. It is now well-known clinically that diabetic patients are prone to develop B-vitamin deficiencies.[50-52] These may result from dietary limitations, but are probably more often related to an increased vitamin requirement of the diabetic individual, possibly due to difficulties in the conversion of these vitamins to coenzymes.[53] Recent experimental evidence has indicated an intimate relationship between the functional state of the adrenal cortex and some of the vitamins of the B-complex, especially pantothenic acid and vitamin B-12.

The Relation of Pantothenic Acid to Adrenal Function in Diabetes

Alloxan-diabetic rats were found to be much more susceptible to a deficiency of pantothenate than were nondiabetic animals.[54] The importance of pantothenic acid in the maintenance of the zona fasciculata of the adrenal cortex of the rat has been well established through the work of Daft and Sebrell,[55] Deane and McKibbin,[56] and Cowgill and co-workers.[57] Pantothenic acid, as an integral part of the coenzyme A system,[58,59] probably plays an important role in the acetylation and biosynthesis of certain oxysteroids by the adrenal cortex. When rats were made deficient in pantothenic acid, they demonstrated adrenal cortical insufficiency with respect to glucocorticoids. Thus, such deficient animals display a decreased urinary excretion of steroids, increased insulin sensitivity,[60] failure to demonstrate eosinopenia following corticotropin administration but prompt response to cortisone,[61] and an atrophic adrenal cortex with zona fasciculata depleted of lipoid vacuoles.[56] It is evident that this is a picture closely resembling that described above in many of the diabetics without retinopathy.

The question naturally arose at this point whether a pantothenate deficiency might account for the adrenal

*The cortisone used in these experiments was supplied by Merck & Co., Inc., Rahway, N. J.

†The corticotropin used in these experiments was provided by Upjohn & Co., Kalamazoo, Mich.

insufficiency found in some of the diabetics without retinopathy. Since all the findings in the deficient animal were promptly reversed by pantothenate, it was most important to determine the effect of pantothenate administration in diabetics without retinopathy who failed to demonstrate any eosinopenia following repeated corticotropin administration. Eleven such patients were given calcium pantothenate* either intramuscularly in 100- to 200-mg. doses or by mouth in doses of 500 to 1000 mgs. Table 9 summarizes the results of such therapy. In 8 of the 11 patients pantothenate administration rapidly normalized the eosinopenic response to corticotropin. Such patients remained responsive to ACTH for periods of six weeks to three months and then slowly lapsed into their unresponsive state. In 2 patients (W.H. and R.V.) of this series who exhibited an eosinopenic response to ACTH only after pantothenate administration, urinary oxysteroid excretion after corticotropin was measured before and after pantothenate administration. In both instances associated with the normalization of the eosinopenic response, under the same conditions of corticotropin stimulation, the urinary steroid excretion rose significantly (Table 10).

It is apparent, therefore, that the defective adrenal cortical function of some diabetics can be attributed to a relative deficiency of pantothenate. On the other hand these patients are not sufficiently deficient in pantothenic acid to demonstrate any marked alterations in their ability to acetylate sulfadiazine. It has been shown, however, that in pantothenate-deficient rats the adrenal cortex can be depleted of coenzyme A long before the liver is affected, and that hypofunction of the adrenal cortex can precede other defects.[62] The pantothenate status of some diabetic patients seems to fall into this marginal state of deficiency.

The fact that 8 of 11 diabetics without retinopathy with hypofunction of the adrenal cortex, as measured by the Thorn test, were promptly normalized by the administration of pantothenate provides evidence for a deficiency of this B factor in some members of this group of diabetics. It also indicates a probable role of pantothenate in the functional state of the adrenal cortex of man. The possibility of clinical trial of pantothenate in various other adrenocortical insufficiencies is most intriguing. Strauss and Brokaw[63] reported that some pernicious anemia patients are resistant to corticotropin-induced eosinopenia. Similar findings have been reported by Rivas[64] in patients suffering from sprue.

*The calcium pantothenate used in these studies was provided by Merck & Co., Inc., Rahway, N. J.

TABLE 9

Effect of pantothenate on eosinopenic response to corticotropin in diabetics without retinopathy

Patient	Per cent Fall in Eosinophils 4 Hours after 25 Units of ACTH	
	Before Pantothenate*	After Pantothenate*
B.J.	0	82‡
	0	60
R.C.	0†	75‡
G.R.	0	88‡
C.B.	0	78‡
R.D.	0	100‡
	0	100
R.W.	0	100§
W.H.**	0	100§
R.V.**	0	100§
D.L.	0	36§
		40‡
C.N.	0	0‡
M.F.	0	0†‡
	0	35‡

* Where more than one value is given, this indicates repeated tests.
† Eosinophil count rose after ACTH.
‡ 100-200 mg. of calcium pantothenate subcutaneously.
§ 500-1000 mg. of calcium pantothenate orally.
** See Table 10 for oxysteroid excretion determined at same times as eosinopenia.

TABLE 10

Effect of pantothenate* on urinary excretion of oxysteroids following corticotropin† in diabetics without retinopathy

Patient	24-Hour Oxysteroid Excretion (in Micrograms)	
	Before Pantothenate	After Pantothenate
W.H.	500	1730
R.V.	232	1960

* A single oral dose of 1000 mg. of calcium pantothenate.
† 25 U.S.P. units of corticotropin given intramuscularly at 0, 4, and 8 hours.
See Table 9 for the effects of pantothenate on the eosinopenic response of these two patients.
We wish to thank Dr. A. Bongiovanni for these determinations.

It was therefore of great interest to find that in 2 patients with pernicious anemia and 1 patient with sprue, the failure to respond with eosinopenia to corticotropin was promptly reversed following the administration of a single oral dose of 1000 mg. of calcium pantothenate. The effects of pantothenate in a carefully selected and closely followed group of patients with Addison's disease might prove most revealing.

Another attractive possibility concerns the utilization of metabolic antagonists of this vitamin (for example, omega-methyl pantothenic acid[65,66] in an attempt to decrease the activity of the adrenal cortex in such con-

ditions as Cushing's syndome, hypertension, and prostatic carcinoma, and perhaps in diabetic retinopathy. It is obvious that many more data are needed to establish the validity of such highly speculative suggestions.

The Possible Role of Vitamin B-12 in Diabetic Retinopathy

The interrelationships in animals of vitamin B-12 metabolism, diabetes, and adrenocortical hormones are just beginning to be realized experimentally. Thus, vitamin B-12-deficient animals exhibit hyperglycemia,[67] and on the other hand, chronic alloxan diabetes depletes the animals of vitamin B-12.[68] The administration of vitamin B-12 labeled with radioactive cobalt 60 results in a relatively high concentration of radioactivity in the pancreas, kidneys, and adrenals of experimental rats. Cortisone administration increases the turnover of vitamin B-12 in all organs studied and results in a markedly increased excretion of B-12 in the urine.[68] Furthermore, in rats, vitamin B-12 has been demonstrated to counteract almost completely such cortisone effects as thymus atrophy, alopecia and inhibition of growth.[69] It is therefore evident that vitamin B-12 metabolism is intimately related both to the diabetic state and to the function of the adrenal cortex.

Becker, Lang, and Chow[68] have applied a B-12 tolerance test to normal and diabetic patients. This consisted of the intramuscular administration of 50 *u*g. of vitamin B-12 and the subsequent determination of the 8-hour urinary excretion of the vitamin, either microbiologically[70] or by labeling with radioactive cobalt 60.[71] Sharply delineated differences were noted between diabetics with retinopahy and those without it.[68] Thus, the diabetic patients without retinopathy excreted an average of 4.2 *u*g. of vitamin B-12 in their urines, much less than did the nondiabetic patients (average 9.6 *u*g.), and resembled chronic alloxan-diabetic rats or vitamin B-12-deficient animals. The diabetics with retinopathy excreted enormously more (average 19 *u*g.) than did those without it, and resembled the cortisone-treated nondiabetic animal or patient. Furthermore, when testosterone cyclopentyl propionate[72] (Depotestosterone*) was administered for several weeks to diabetics with retinopathy, their test dose excretion of vitamin B-12 was reduced to the nonretinopathy levels (Table 11).[68]

The decreased excretion of a test dose of vitamin B-12 by diabetic patients is consistent with a deficiency or abnormal retention of this vitamin associated with the diabetic state. The increased excretion of a test dose of B-12 by diabetics with retinopathy provides further suggestive evidence that excessive activity of the adrenal cortex is associated with this syndrome. The increased secretion of adrenocortical hormones probably masked the latent vitamin B-12 defect of this group of diabetics and resulted in an increased excretion of the test dose. This excretion pattern is entirely comparable to that noted in normal patients following the administration of cortisone. Cortisone has also been reported to produce an increased excretion of vitamin B-12 even in animals made markedly deficient in the vitamin, thus aggravating the deficiency state.[73] The administration of testosterone presumably decreased the endogenous production of adrenocortical hormones in the diabetics with retinopathy and revealed their true vitamin B-12 status. At any rate, the vitamin B-12 test dose excretion provides a useful index for the presence or absence of retinopathy in the diabetic. It also appears to support the thesis of a difference in function of the adrenal cortex in these two groups of diabetic patients.

TABLE 11
Excretion of vitamin B-12 following intramuscular test dose of 50 microgm.[68]

	No. of Patients	Micrograms (average) Excreted
Nondiabetics	6	9.6 ± 1.4
Diabetics:		
Without retinopathy	13	4.2 ± 1.7
With retinopathy	22	19.0 ± 2.1
With retinopathy following testosterone	11	4.5 ± 1.9

As discussed previously, alloxan diabetes potentiated the cortisone-induced renal lesions in the rabbit (Table 8). Since an abnormal retention of a test dose of vitamin B-12 was found to be associated with the diabetic state both in animals and in man, Becker and coworkers[74] investigated the effect of the omission of supplementary vitamin B-12 and aureomycin from the diets of cortisone-treated (8 mg./day) nonalloxanized rabbits. Under such experimental conditions, the incidence of renal lesions rose to almost 100 per cent (Table 12). However, the parenteral administration of massive doses of vitamin B-12 failed to suppress the lesions in one-third of the rabbits. There was also no evidence of any improvement of clinical diabetic retinopathy following vitamin B-12 administration.[74,75] Furthermore, a series of 20 patients with diabetic retinopathy treated with testosterone and vitamin B-12 for over nine months failed to show improvement.[76] Nevertheless, it seems possible that a defect in the metabolism or binding of vitamin B-12 as well as hyperfunction

*The depotestosterone used in this study was supplied by Dr. Hailman of Upjohn & Co., Kalamazoo, Mich. It was used in intramuscular doses of 100-200 mg. every two to three weeks.

TABLE 12
Incidence of cortisone*-induced renal lesions in rabbits in relation to diet[74]

	No. of Rabbits	No. of Lesions
Regular diet†	50	16 (32%)
Diet without vitamin B-12	25	24 (96%)

* Cortisone acetate, 4 mg./kg./day for 21 days.
† Contained 5 mg./ton of vitamin B-12 and 3.6 gm./ton of aureomycin.

of the adrenal cortex contributes to the pathogenesis of some of the complications of diabetes.

Vitamin B-12 has been reported to alleviate some cases of diabetic neuropathy.[51,75] There are also many similarities between the neuropathy of diabetes and of pernicious anemia.[75,77] It was therefore of interest to explore the relationship between the neuropathy and the retinopathy of diabetes. If an abnormality of vitamin B-12 utilization or availability should prove to be causally related to the development of the neuropathy, the coexistence of neuropathy and retinopathy would provide further evidence for a disordered vitamin B-12 metabolism in the diabetic with retinopathy. Henderson et al[78] reported that diabetic neuropathy occurred more frequently among the Kimmelstiel-Wilson group of diabetics than among diabetic patients without nephropathy. Collens[79] reported that 93 per cent of all diabetics have some impairment of vibratory sense. Moreover, the defect was much more marked in those diabetics with proteinuria.[80] Whereas 76 of the 100 diabetic patients with proteinuria had less than 10 per cent of normal vibratory sense, only 2 of the 100 diabetics without proteinuria had so severe an involvement. Furthermore, there are clinical reports that the neuropathy of the diabetic, like the retinopathy and the nephropathy, is aggravated by infection and pregnancy, and is correlated with the duration of the diabetes rather than its severity.[81] A review of the histories of all cases of diabetic neuropathy in the files of the Johns Hopkins Hospital revealed that over 90 per cent of such patients had diabetic retinopathy (Table 13).[82] This is perhaps additional evidence for the possible association of a deficiency or abnormal metabolism of vitamin B-12 with the retinopathy of diabetes.

TABLE 13
Incidence of diabetic retinopathy in patients with diabetic neuropathy

	No. of Patients	No. with Diabetic Retinopathy
Sancetta (1951)[75]	12	10 (83%)
Becker & Maengwyn-Davies (1952)[82]	49	46 (94%)

The question naturally arose at this point in the investigation why diabetic retinopathy is not seen frequently in patients with untreated pernicious anemia. It is true that retinal capillary aneurysms were described in pernicious anemia at autopsy before they were first found in diabetic retinopathy.[7] Flat preparations of the retinas revealed microaneurysms in only 2 of 8 available retinas from patients with untreated pernicious anemia in the autopsy files of the Johns Hopkins Hospital.[83] Neither of these patients had any history of diabetes. Strauss and Brokaw[63] have pointed out that some pernicious anemia patients have adrenocortical insufficiency, as demonstrated by a failure to obtain an eosinopenic response to corticotropin, but exhibit a prompt fall of circulating eosinophils after cortisone administration. This decreased function of the adrenal cortex was not improved by remission or by therapy with vitamin B-12. Thus, patients with pernicious anemia resemble the diabetics without retinopathy in their adrenocortical capacities.

The similarity of the adrenal status of these two groups is further evidenced by the demonstration in 2 pernicious anemia patients, with adrenals refractory to corticotropin, of a prompt eosinopenic response to this hormone after the administration of pantothenate. Furthermore, the adrenals of pernicious anemia patients at autopsy are much more lipoid-depleted than are the normals or the diabetics with retinopathy, and again resemble the diabetic without retinopathy (Tables 2 and 14). Perhaps it is this adrenal insufficiency that protects some pernicious anemia patients as well as some diabetics from retinopathy.

TABLE 14
Lipoid vacuolization of zona fasciculata of adrenal cortex

Patients	No. of Patients	Vacuolated	Nonvacuolated	Unclassified
with pernicious anemia	32	12 (38%)	14 (44%)	6 (18%)
Normal*	91	68 (75%)	16 (17%)	7 (8%)

* With no evidence of diabetes or pernicious anemia.

It is of interest in this regard that a vitamin B-12 deficiency alone in animals has failed to produce lesions resembling those described by Kimmelstiel and Wilson unless cortisone was administered.[83] The effects of cortisone on the retinas and kidneys of untreated pernicious

anemia patients would provide a possible clinical experiment under conditions perhaps comparable to those in the rabbit experiments.

The problem of why the apparent deficiency of vitamin B-12 in the diabetic patient does not result in pernicious anemia or megaloblastic anemia is much more difficult to rationalize at this time. The suggestions that in addition to a vitamin B-12 deficiency in the pernicious anemia patients there are "inhibitory factors,"[84] "toxic phenolic substances,"[85,86] or "hemolytic factors,"[87] or a "constitutional predisposition,"[88] do not entirely resolve the dilemma. Perhaps the diabetic is not truly deficient in vitamin B-12, but retains an abnormal amount of a test dose for other reasons. However, it is true that a deficiency of vitamin B-12 alone does not produce pernicious anemia in experimental animals,[88] and gastrectomy in patients without pernicious anemia does not often result in pernicious anemia. On the other hand, pernicious anemia does occur more often in diabetic patients than in the general population. Thus, Beckert[89] found pernicious anemia in 1 per cent of 900 diabetics. Furthermore, some 40 per cent of diabetics are reported to have achlorhydria.[90] The similarities of the neurologic manifestations of diabetes and pernicious anemia have been pointed out.[75] It is evident that considerably more knowledge is needed about both pernicious anemia and diabetes, as well as their interrelationships, before a more satisfactory answer to this thorny problem can be formulated.

At any rate, it seems likely that adrenocortical function, diabetes and a disordered vitamin B-12 metabolism act together in producing the lesions of diabetic retinopathy and nephropathy, possibly by means of their effects on some other metabolic system. Changes have been noted in the serum mucoid and lipoprotein levels in patients with this disease. The possibility exists that these findings are the signs of disordered metabolic pathways upon which converge the interactions of the hormones of the adrenal cortex, diabetes, and vitamin B-12.

SERUM POLYSACCHARIDES IN DIABETES

McManus[91] has suggested that the source of the hyaline material which is deposited in the glomeruli might be an abnormal circulating polysaccharide. Friedenwald[11] pointed out that a disturbance in mucoid metabolism in diabetics with retinopathy might explain much of the pathology of the retinal and renal lesions. Jacobs[92] has described a parallelism between the variations of the bound glucosamine and the glucose levels of diabetics in response to insulin. Berkman et al[93] have recently demonstrated an increased level of certain polysaccharide substances in the sera of the Kimmelstiel-Wilson group of diabetic patients.

It is fascinating to speculate about a disordered metabolism of mucoids which could result in disturbances of the basement membranes of the capillaries of the retina and kidney as well as an increased capillary fragility,[94] and might also account for the abnormal deposition of polysaccharides in these defective areas. The current data suggesting a role of the adrenal cortex in the pathogenesis of this disease entity do not negate such a thesis. Layton[95] has demonstrated that cortisone inhibits the transformation of inorganic sulfate to mucoid sulfate in animal tissues. The serum hyaluronidase inhibitor has been studied extensively by Glick and co-workers.[96] These experiments resulted in the demonstration of a close correlation of the concentration of circulating hyaluronidase inhibitor with the level of activity of the adrenal cortex, increasing in pregnancy or after cortisone administration, and decreasing following adrenalectomy. Furthermore, the increased serum polysaccharides of the diabetic with glomerulosclerosis were found by Rifkin and co-workers[93] to be further elevated following the administration of corticotropin. Thus, the data on polysaccharide disorders in diabetic retinopathy and nephropathy are not mutually exclusive of the adrenal hypothesis, but, in fact, provide a possible mechanism for the role of hormones of the adrenal cortex in the pathogenesis of this disease process.

SERUM LIPOPROTEINS IN DIABETES

Another aspect of the disordered metabolism of the diabetic has been approached by the observations of Engelberg[97,98] and others,[99] on serum lipoproteins. These workers noted a marked increase in the S_f 12-20 class of circulating lipoproteins occurring in diabetic patients with retinopathy and nephropathy. Simon[100] first stressed the lipohyaline nature of the deposits in intercapillary glomerulosclerosis. Wilens and co-workers[101] in an extensive study of glomerular fat have demonstrated the inordinately high lipid content of the Kimmelstiel-Wilson glomerular nodules, and the possibility of a fatty deposit as one of the initial occurrences in the development of these pathologic defects. Rifkin and co-workers[102] have illustrated the importance of the characteristic lipoid droplets in the urinary sediment for the early diagnosis of diabetic glomerulosclerosis. The presence of lipids in the walls of retinal capillary aneurysms can be readily demonstrated.[103] Thus, an equally attractive thesis can be postulated for a disordered metabolism of lipoproteins as for mucoids.

However, it should be noted that other diseases with elevated serum lipoproteins such as myxedema, nephrosis, and atherosclerosis[104] do not demonstrate the specific lesions of diabetic retinopathy and Kimmelstiel-Wilson renal disease. This nonspecificity of elevated serum lipoproteins would therefore suggest an additional factor in this disease process, such as a mucopolysaccharide defect, with associated alterations and depositions of lipoproteins.

It is of interest in regard to a possible abnormality of lipoprotein metabolism associated with diabetic retinopathy that alloxan-diabetic animals are more susceptible to lipemia,[105] and that cortisone administration to rabbits results in a marked lipemia,[106,107] with elevation of lipoprotein components of the S_f 10-30 class. Furthermore, cortisone has been postulated to produce a metabolic block in the breakdown of lipoproteins in rabbits at the level of the S_f 40-80 class with the accumulation of lipoproteins of higher S_f rate in the serum.[108] Alloxan diabetes in rabbits likewise blocks the conversion of lipoproteins of S_f 80-100 and above into lipoproteins of lower S_f classes.[109] Thus, alloxan diabetes and cortisone, which act together to produce renal lesions in the rabbit, also behave similarly in interference with lipoprotein metabolism. Increased serum S_f 12-20 lipoproteins have been noted associated with the stress induced in patients by pyrogen administration,[110] and in rabbits by cold injury.[111] Furthermore, testosterone produces a depression of the elevated serum lipoproteins in diabetic patients.[112] It is thus apparent that changes in adrenocortical activity are associated with alterations in serum lipoproteins and that the abnormal levels of serum lipoproteins reported in the Kimmelstiel-Wilson group of diabetic patients is entirely consistent with the hypothesis of a role of the adrenal cortex in this disease process.

The administration of cortisone to animals produces a fatty liver and makes such animals more susceptible to induced liver damage.[113] Vitamin B-12, on the other hand, has lipotropic properties and has been shown to protect animals against the liver damage caused by carbon tetrachloride, chloroform, choline deficiency, high-fat diet, etc.[114-116] It has been demonstrated by liver biopsy that there is a higher incidence of fatty livers in diabetic patients who are insulin-resistant, especially those with diabetes of long duration.[117] The studies on possible lipoprotein abnormalities in diabetic retinopathy and nephropathy are thus far from independent of the changes in vitamin B-12 metabolism, mucoids, and the adrenal cortex demonstrated in this disorder.

The synthesis of all of these heterogeneous but related findings into a unified concept of the pathogenesis of the vascular lesions of diabetic retinopathy and glomerulosclerosis must await further data from the concerted efforts of the biochemist, the endocrinologist, the nutritionist, the pathologist, and the ophthalmologist. At present there is no outstanding evidence to negate the tentative working hypothesis of a role of relatively increased function of the adrenal cortex in the pathogenesis of this disease complex. If such a thesis, although admittedly tenuous, stimulates various better equipped workers to conduct critical studies, it will have served its purpose, and the perplexing problems of this metabolic disorder may be one small step closer to solution.

SUMMARY

1. In diabetic patients at autopsy, there is a close correlation in occurrence, appearance, and staining characteristics between the retinal capillary microaneurysms and the renal glomerular lesions described by Kimmelstiel and Wilson.

2. There is increasing evidence of a role of the adrenal cortex in the pathogenesis of this retinopathy-nephropathy syndrome. This tentative hypothesis is based upon:

a. *Suggestive clinical observations* of a decrease of certain adrenocortical capacities in some diabetics without retinopathy, and a relative increase of some aspects of adrenocortical function in diabetics with retinopathy.

b. *Therapeutic reports* of possible improvement of diabetic retinopathy by decreasing the activity of the adrenal cortex.

c. *Histopathologic data* of relative adrenal hypertrophy, excessive lipoid vacuolization of the zona fasciculata, and an increased incidence of adrenocortical adenomas in the nephropathic group as compared with the nonnephropathic.

d. *The experimental production* of lesions resembling those of Kimmelstiel-Wilson nephropathy in alloxan-diabetic rabbits by the administration of cortisone or corticotropin.

3. Recent studies have indicated an intimate relation of both diabetes and adrenocortical function with some vitamins of the B complex.

a. Pantothenate has been found necessary for maintaining the integrity of the adrenal cortex, perhaps by its role in acetylation (coenzyme A). Thus, pantothenate-deficient rats have decreased adrenocortical capacity and resemble some diabetics without retinopathy. Administration of pantothenate results in prompt improvement in both instances.

b. Cortisone mobilizes vitamin B-12 from the tissues

and increases its excretion in the urine.

c. Omission of supplementary vitamin B-12 and aureomycin from the diet potentiates the cortisone-induced renal lesions in rabbits; however, parenteral administration of vitamin B-12 to animals on this nonsupplemented diet fails to protect.

d. The test dose excretion of vitamin B-12 by diabetics with retinopathy differs markedly from those without retinopathy. This difference is compatible with an abnormal retention of administered vitamin B-12 associated with the diabetic state, but masked in the patients with retinopathy by the excessive adrenocortical activity.

4. Some of the possibilities are discussed for a disordered metabolism of mucoids or lipoproteins as pathways of interaction of diabetes, vitamin B-12, and hormones of the adrenal cortex.

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Diurnal Rhythm in Severe Diabetes Mellitus

The Significance of Harmoniously Timed Insulin Treatment

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In 1928, my attention was aroused by the behavior of the blood sugar and sugar excretion in a diabetic patient.[1] It was noted that the alimentary hyperglycemia almost disappeared, and that the blood sugar gradually dropped to a low level, about noon, even though food was given to the patient. To study this phenomenon more closely, a series of clinical experiments was carried out with diabetics and normal subjects receiving the same food and living under identical experimental conditions.[2] In this study as in the first case, the diurnal variations both of the glucosemia and of the glucosuria were observed to coincide more or less distinctly. Since the diurnal variations of the blood sugar coincided with those of the urine sugar, it was evident that a correct picture of the diurnal rhythm might emanate from observation of the urine sugar only.[3]

On the basis of these studies, during the first year I used a method of insulin treatment based on the diurnal variations of the urine sugar excretion.[4]

CHANGES IN EXCRETION OF KETONE BODIES

In the early phase of these studies, it was observed that the insulin treatment was sometimes not quite satisfactory, especially in cases of severe diabetes with acidosis. My attention was attracted by the behaviour of the ketone bodies, in particular by the excretion of beta-hydroxybutyric acid.[5] It was found that with unchanged food intake and decreasing insulin dosage the sugar excretion remains fairly stable, while there is a rapid rise in the excretion of beta-hydroxybutyric acid.[6] It was also noted that on fasting days without insulin, there occurred a rhythmical excretion of beta-hydroxybutyric acid, which did not coincide with the urine and blood sugar variations.[7]

The above evidence tends to show how important it is to examine every diabetic as an individual case, and to analyse this case in detail if the treatment is to be successful. The knowledge of whether or not ketone bodies are formed in a given case is essential, as is precise information as to the variations in the excretion of acids and sugar in conformity with the diurnal rhythm. If there is ketone body formation, it is also important to appraise the ammonia-forming capacity of the kidneys, as this is instrumental to the protective mechanism against acidosis and coma. If the ratio of beta-oxybutyric acid to ammonia is higher than one, the case should be considered very grave with impending danger of coma.

CLASSIFICATION OF CASES

At present, I analyse the diabetic state in patients according to the above principles. When the diabetic state is studied with such analyses, three separate types of diabetes can be differentiated, namely: (1) Diabetes characterized by ketone body excretion and sufficient ammonia formation. In these cases there is no impending danger of coma. I have termed this form *Type* A (2) Diabetes with ketone body excretion and poor ammonia formation. This is a grave type, and if insulin treatment is *not* instituted, coma will rapidly ensue. This is my *Type* O, meaning no day without insulin. (3) Diabetes without ketone body excretion. This is a mild form; there is no danger of coma. I name this form *Type* B.

The following three figures show graphs based on the average of 25 cases of different types of diabetes. The cases were selected at random and demonstrate the characteristic phenomena. Figure 1 relates to Type A. It will be seen that on a fasting day the urine sugar shows rhythmical variations, but its amount decreases gradually. The beta-oxybutyric acid excretion is not lessened and subject to marked rhythmical variations. Sufficient ammonia is being formed. The blood sugar shows no signs of rhythm. Food intake produces a rise in the urine sugar excretion, whereas ammonia and beta-hydroxybutyric acid are eliminated in unchanged amounts.

Figure 2 relates to Type O. The rhythmical variations

Read at the Annual Meeting of the American Diabetes Association in Chicago, June 8, 1952.

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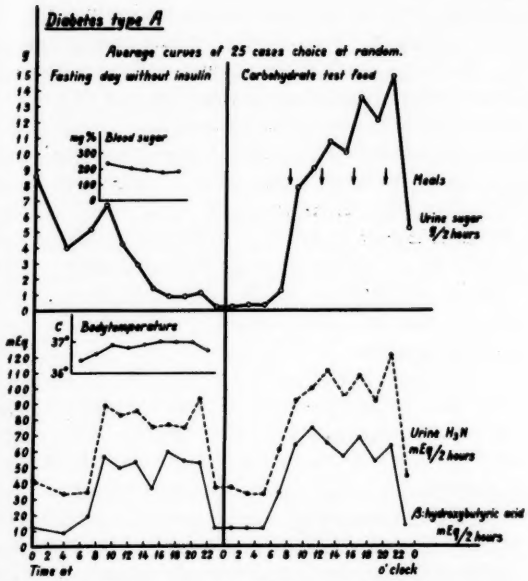

FIGURE 1. Average curves of 25 cases of diabetes TYPE A, selected at random. Diabetes with ketone body formation and satisfactory ammonia production.

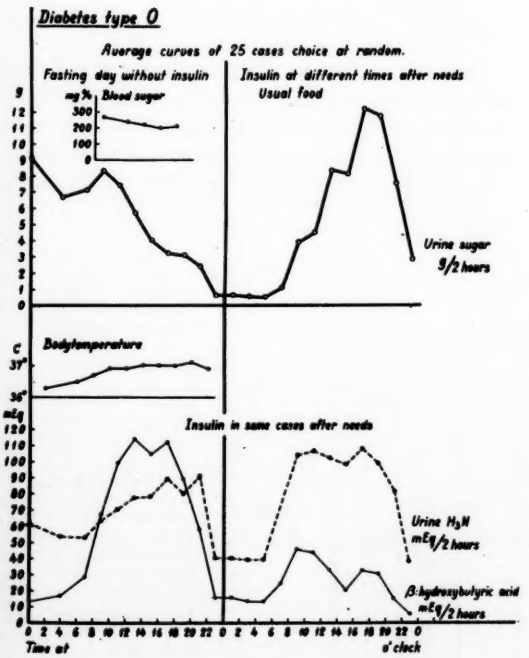

FIGURE 2. Average curves of 25 cases of diabetes TYPE O, selected at random. Diabetes with ketone body formation and poor ammonia formation.

of sugar and beta-hydroxybutyric acid appear to be the same as in Type A. Ammonia formation is here poor. There is grave danger of precoma, and *insulin must be given immediately.* It will repress the excretion of beta-oxybutyric acid and remove the danger of coma. The sugar excretion rises when food is given.

Figure 3 represents Type B. There is no excretion of beta-hydroxybutyric acid. The sugar excretion ceases on fasting days but returns when food is taken. The diurnal rhythm of the sugar excretion is well marked. The body temperature shows a rhythm similar to that of the sugar excretion.

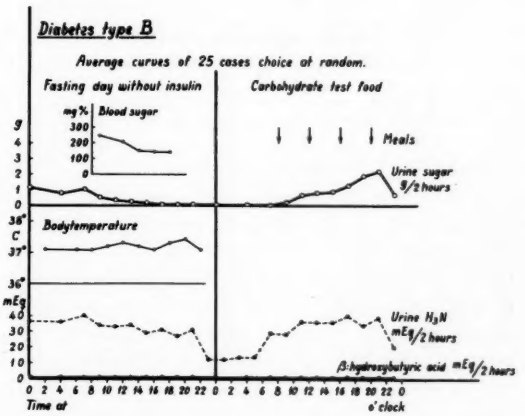

FIGURE 3. Average curves of 25 cases of diabetes TYPE B, selected at random. Diabetes without formation of ketone bodies.

During the last twenty years I have studied roughly 4,000 cases of diabetes and analysed them according to the above principles, that is, grouping them in the three groups described in the foregoing. I was interested in the incidence rates of the separate types at different ages. A statistical analysis was made of 2,116 cases. (Figure 4.) This study disclosed that Type O is frequent in childhood, while there are only a few cases in old age. The opposite is true as regards Type B; it is most common in the aged, and there are few cases among children. Type A lacks a characteristic age distribution.

CASE REPORT

Lastly I should like to give an example and to illustrate the practical application of this method of treating diabetes.

The patient was a woman, aged 46, who had had diabetes since the age of 43. For 2 years she had been

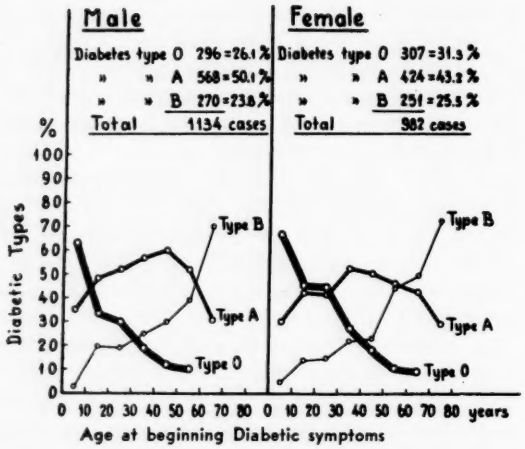

FIGURE 4. Incidences of the separate diabetes types within different age groups (age at the onset of disease).

treated with a mixture of zinc protamine and ordinary insulin, later retard insulin, *once* a day. In these years she had frequent hypoglycemic reactions but if the insulin dosage was decreased there was a tendency to acidosis. The first examination failed to disclose excretion of beta-hydroxybutyric acid. When the amount of insulin was reduced, a periodic excretion of beta-hydroxybutyric acid was found to commence. This observation is shown in Figure 5. The graph illustrates the diurnal rhythm of the beta-hydroxybutyric acid excretion, and *once this rhythm was known, correction of the treatment was easy.* The insulin administration was adapted to the rhythmical excretion of beta-hydroxybutyric acid, and two days after institution of the harmoniously timed insulin treatment, the diabetes was under perfect control. In the following days, the amount of insulin was adjusted to the needs of her normal diet and life. A few days after institution of the harmoniously timed insulin treatment, a remarkable general recovery was noted, and the patient no longer complained of lassitude and cardiac discomfort, from which she had suffered earlier. Hence it is easy to follow the changes in the need of insulin by examining day and night specimens of urine and by recording the weight.[7] My studies have shown that harmoniously timed insulin treatment also has practical advantages.

Before ending this paper I should like to recall the fact that the phenomenon of diurnal rhythm is connected with the rhythmical liver function. The diurnal liver rhythm was discovered in 1927 by the Swedish histologist, Erik Forsgren.[8] Forsgren's work was confirmed and extended by the Swedish experimental histologist, Hjalmar Holmgren, who carried out fundamental investigations. I deplore the all too early death of this dear friend. For nearly 20 years we worked in close collaboration to elucidate more clearly the diurnal rhythm governing the metabolic processes in diabetes.

SUMMARY

The diurnal rhythm of carbohydrate metabolism as manifested by periodic glycogen formation in the liver as well as by the fluctuations of the blood and urinary sugar in diabetics, is also to be observed in the production and elimination of ketone bodies during fasting,

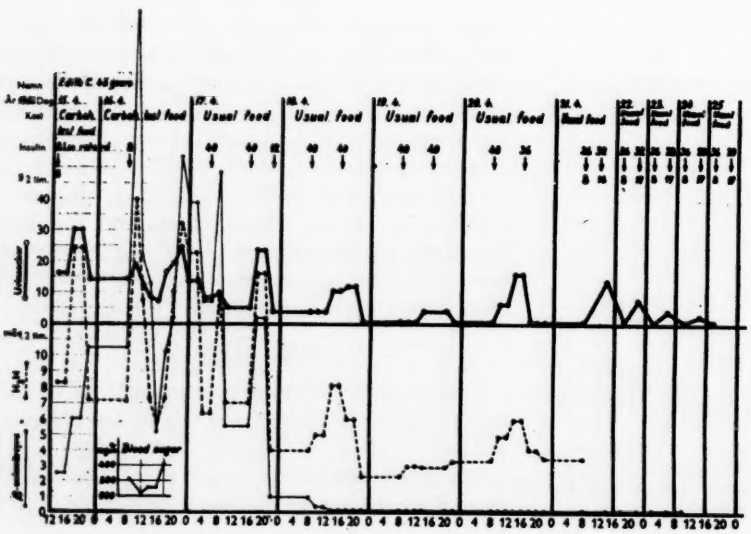

FIGURE 5. A case of severe diabetes showing the rates of urinary excretion of sugar, ammonia and beta-hydroxybutyric acid at two-hour intervals. Previous treatment (one single injection of insulin a day) disharmonious. Adaptation of a second dose of insulin to the developing wave of beta-hydroxybutyric acid resulted in harmoniously timed insulin treatment with clinical and laboratory evidence of improvement.

not paralleling the changes of glycosuria in severe cases of diabetes. To obtain a conception of the diabetic state, it is essential to know whether or not ketone bodies are formed in a given case, and whether the formation of ammonia is sufficient as a protective mechanism against acidosis and coma. Without insulin administration, three types of diabetes will be found, characterized by (a) ketone body formation with sufficient ammonia excretion during fasting; (b) no ketone body formation during fasting; and (c) ketone body formation with insufficient ammonia excretion during fasting. Individual adjustment of insulin dosage and harmonious timing of insulin injections to the waves of the periodic excretion of beta-hydroxybutyric acid are indispensable for successful treatment of severe diabetes mellitus.

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DISCUSSION

CHARLES H. BEST, M.D., (*Toronto*): In opening the discussion of Dr. Jakob Möllerström's clear presentation of the significance of harmoniously timed insulin dosage in the treatment of severe diabetes, I shall have to admit that I have probably been chosen, not because of my knowledge of this subject but because I am a friend of Doctor Möllerström. I have visited his clinic and laboratories in Stockholm and can bear witness to the devoted efforts which he has made to improve the welfare of Swedish diabetics. I am familiar with Dr. Eric Forsgren's work on the diurnal rhythm of liver function and I believe that these constitute a very interesting and real physiological problem. I did not know Doctor Forsgren personally, but I was well acquainted with Dr. Hjalmar Holmgren who did so much, along with Doctor Möllerström, to work out the details of these rhythmical changes. I had a very great respect and admiration for Doctor Holmgren and had hoped to have him spend some time in my laboratory as a Visiting Professor.

The most interesting part of Doctor Möllerström's presentation to me is the rhythmical peak in beta-hydroxybutyric acid excretion in his patients. I am informed by Dr. O. Sirek, who worked for several years with Doctor Möllerström and who is now on my staff in Toronto, that he has seen these peaks demonstrated in Doctor Möllerström's patients with great regularity and clarity. Indeed, that is what Doctor Möllerström has shown us to-day. I have gone over his data several times in Stockholm and in Toronto. As a physiologist I would, of course, like to know a lot more about the actual cause of these rhythms. I am not prepared to believe at the moment that they are caused by changes in gravitational forces or by any celestial manifestations! I feel that they merit careful biochemical and physiological study and that a simple explanation can probably be found. In the meantime, our friend Doctor Möllerström is trying to improve the treatment of diabetes by spacing his doses of insulin so that ketone body formation will be kept under control for as large a part of the day as possible. Doctor Möllerström does not use rigid dietary control in the treatment of his cases but his procedure does not come under the term "free diet." I would predict that, if we could produce a more physiological insulin which would decrease the daily sugar excretion without the threat of hypoglycemia, Doctor Möllerström would be one of the first to use it.

Measurement of the Response to Insulin

*Louis K. Alpert, M.D., Alvin E. Parrish, M.D., and Karl P. Kolb, M.D.**

In the present study a comparison has been made of the responses to insulin in diabetic and nondiabetic patients. The approach to the measurement of the action of insulin was based on its capacity to increase the rate of utilization of administered glucose.

METHOD

In order to achieve a relative degree of constancy with respect to the various dynamic factors involved in carbohydrate metabolism, a continuous intravenous infusion of 5 per cent glucose in water was administered to fasting patients, at a steady rate of approximately 240 mg. of glucose per min., during a 2-hr. period. Venous blood samples were drawn before, and at intervals of 30, 60, 75, 105, and 120 min. after the start of the infusion. The blood glucose concentrations were determined by a modification of the Somogyi-Nelson technic.[1]

To measure the effect of insulin, 5 units of regular insulin per sq. m. of body surface were injected intravenously, 60 min. after the start of the 2-hr. glucose infusion. In the diabetic patients who had been receiving insulin previously, all insulin was withheld during the 24 hrs. preceding the test.

RESULTS

Observations have been made in a total of 97 individuals. These included 54 diabetics (11 with glucose alone, and 43 with glucose and insulin), and 43 nondiabetics (7 with glucose alone, and 36 with glucose and insulin).

The curves of the mean values of the blood glucose concentrations obtained in the nondiabetic individuals are shown in Figure 1, and those of the diabetic patients in Figure 2. In comparing the groups of nondiabetics and diabetics who were given glucose without insulin, it is apparent that the mean blood glucose concentrations rose (1) more rapidly, and (2) for a longer period of time before achieving relative stability, in the diabetic than in the nondiabetic group. After the administration of insulin, the mean blood glucose values decreased more rapidly in the diabetic group than in the nondiabetic.

The rate of fall of the blood glucose concentrations,* in terms of mg. per 100 cc. per min., during the 45-min. period following the injection of insulin, was used as the index of response to the administered insulin. The mean value of this index in the diabetic group was 1.67 ± 1.52, and in the nondiabetic one was 1.11 ± 0.49. The greater standard deviation in the diabetic group is a reflection of the wider range of variability observed among the individual indices of these patients (Figure 3). There did not appear to be any positive relationship between the indices of response to insulin in the individual patients and either (1) the levels of the blood glucose concentrations immediately preceding the injection of insulin (Figure 4), or (2) the daily requirements of insulin for clinical control of the diabetes (Figure 5).

DISCUSSION

These observations demonstrate the difficulties inherent in an attempt to measure precisely the action of insulin, in terms of changes in concentration of glucose in the peripheral blood. Even though, with the procedure described, two factors were controlled, namely the administration of glucose and of insulin, the wide variation in the observed responses to insulin would indicate that the alterations in blood glucose levels were undoubtedly influenced by a multiplicity of undetermined endogenous factors. The only conclusion which would appear justifiable from these results is that, under the conditions of the experiments, the apparent responses to

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* This was calculated from the formula for linear regression: Rate of fall $= SXY/Sx^2$, where x = time in minutes and Y = blood glucose concentration.[2]

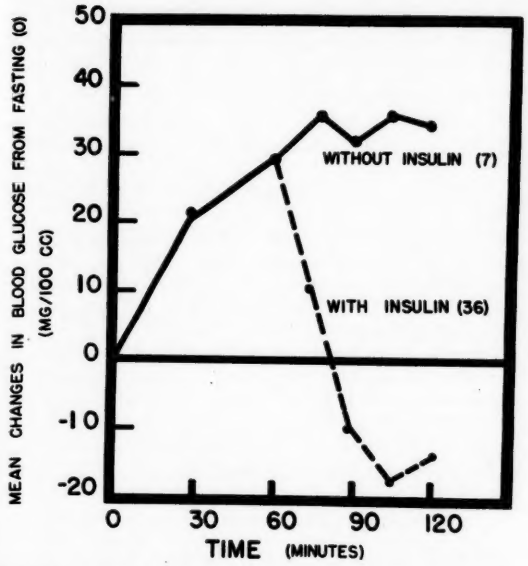

FIGURE 1. Nondiabetic patients. Changes in the mean values of blood glucose concentrations during continuous intravenous infusion of glucose without insulin (solid line), and after insulin (broken line). See text for details.

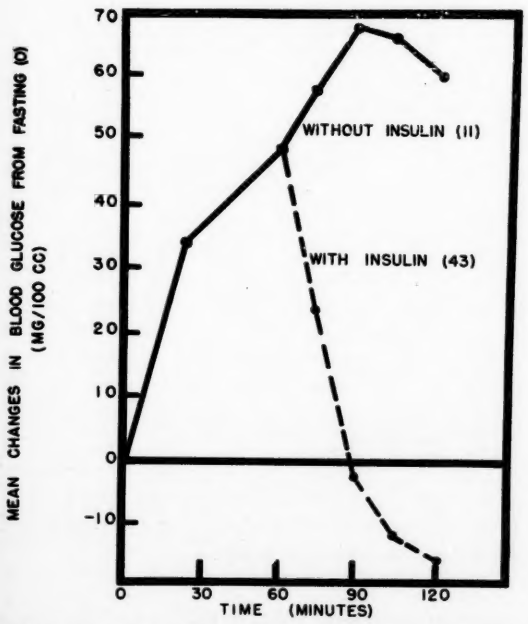

FIGURE 2. Diabetic patients. Changes in the mean values of blood glucose concentrations during continuous intravenous infusion of glucose, without insulin (solid line), and after insulin (broken line). See text for details.

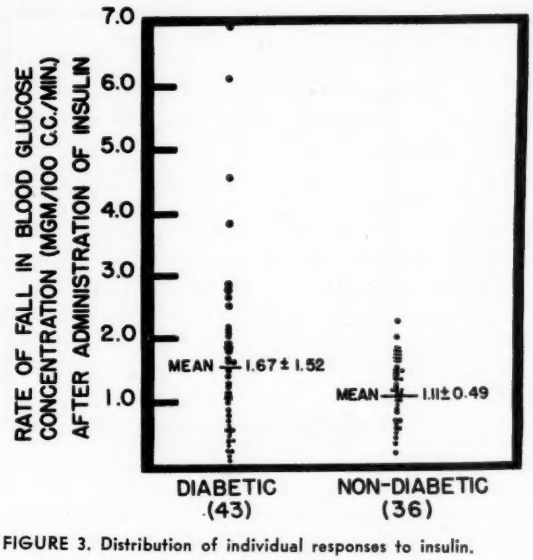

FIGURE 3. Distribution of individual responses to insulin.

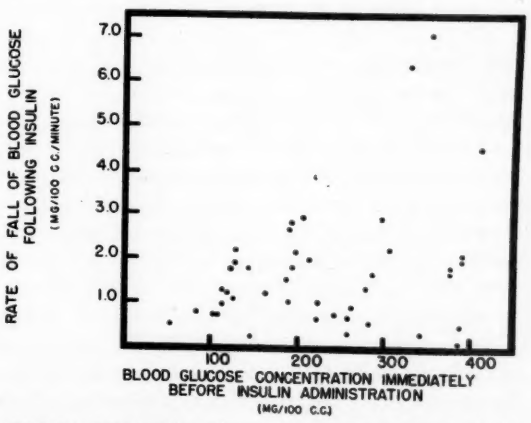

FIGURE 4. Relationship between the responses to insulin in the diabetic patients and their blood glucose levels prior to injection.

insulin in the group of diabetic patients were equal to, or slightly greater than, those observed in the nondiabetic individuals. Therefore, these observations would lend support to the thesis that diabetes mellitus is probably not associated with an inhibition of the peripheral action of insulin.

The generally accepted "inhibitory" effects[3,4] of anterior pituitary and adrenal cortical hormones upon the action of insulin should, perhaps, be reconsidered from the point of view of possible independence of action of the pituitary and adrenal hormones, with respect to gluconeogenesis,[5,6] and of insulin, with regard to glycolysis.

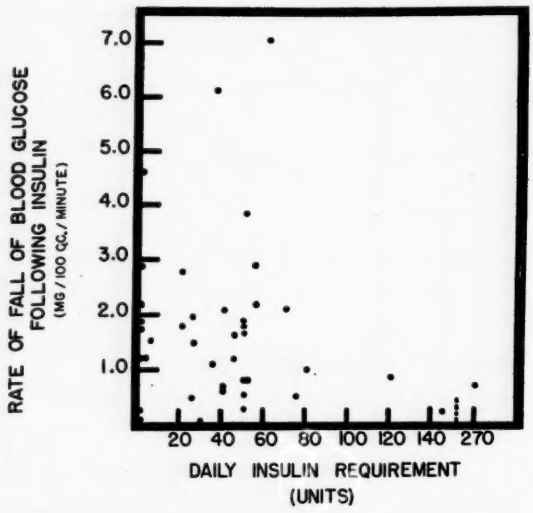

FIGURE 5. Relationship between the responses to insulin in the diabetic patients and their daily clinical requirements.

The measurement of the action of insulin, when limited to the determination of changes in glucose concentration, without the use of isotopically labelled glucose, glucose precursors or glycogen, may be determined as much by the total amount of glucose available from both endogenous and exogenous sources, as by the capacity of each unit of insulin to accelerate the utilization of a specific quantity of glucose.

SUMMARY

1. A comparison has been made, by the methods described, of the changes in blood glucose concentrations in response to the administration of glucose, and of glucose and insulin, in diabetic and nondiabetic patients.

2. The response to insulin which was observed in the group of diabetic patients appeared to be equal to, or slightly greater than, that in the nondiabetics.

3. The relative degrees of response in the individual diabetic patients were apparently unrelated to their daily clinical requirements for insulin, or to the blood glucose levels prior to the administration of insulin.

4. The difficulties inherent in attempting to measure precisely the action of insulin in terms of changes in peripheral blood glucose concentrations are stressed.

5. It is suggested that the apparent "inhibitory" effects of the anterior pituitary and adrenal cortical hormones upon the peripheral action of insulin may be reconsidered from the standpoint of possible independence of the glycolytic activity of insulin and the glyconeogenetic actions of the pituitary and adrenal hormones.

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DISCUSSION

FRANK N. ALLAN, M.D., (*Boston*): This paper recalls to mind my experience when I became a member of the team engaged in insulin research at the University of Toronto in 1922. Professor Macleod assigned to me the task of studying the glucose equivalent of insulin. My approach was to determine the number of grams of glucose utilized per day in relation to the dosage of insulin, the glucose of the diet and other factors.

I found that as the dose of insulin was increased, the effect per unit became less and that as the amount of glucose fed was increased, the effect per unit became greater. I was able to work out logarithmic formulae to show the correlation. But, unfortunately, it proved impossible to use these data as the basis for the assay of insulin as had been hoped, because of the influence of other variable factors. Of course, all of us apply these principles in practice with patients. We know that doubling the dose of insulin does not double its effect; thus patients tend to have protection from the effects of overdosage. We also know that the carbohydrate in the diet can be increased without a proportionate increase in the insulin requirement.

The whole problem of the quantitative measurement of the response to insulin deserves study from every aspect; this may eventually lead to better understanding of the mechanism of insulin action.

HENRY T. RICKETTS, M.D., (*Chicago*): The figures showing the decline in the blood sugar of diabetic patients given insulin indicate a wide range, as Dr. Alpert himself pointed out, the rate of fall varying from 0.01

to 7.0 mg. per 100 cc. per min. It is evident also from these data, that not all diabetics are as sensitive to insulin as the average normal person, although on the whole, most of them seem to be equally sensitive, or somewhat more so.

The situation is a little like that of the insulin content of the pancreas, of which Dr. Wrenshall spoke yesterday. He said that, on the whole, the pancreas of the adult diabetic has about half the insulin content of the normal pancreas, but certainly in some diabetics the pancreas contains even more insulin than the average normal pancreas. So, there is a very wide range in the diabetic individual, as compared with the normal, with respect both to his response to insulin and the insulin content of his pancreas.

I am not entirely sure that we can use Dr. Alpert's results to show that diabetes is primarily a matter of insulin deficiency. He does not claim so in any strong terms, and I think we should keep our minds open on this question.

I hope very much that he will be able to apply this technic, which seems to be a very useful one and which is being employed, I think, by increasing numbers of workers to cases of outspoken insulin resistance.

Nitrogen Equilibrium

One of the most frequent misconceptions is that of the significance of nitrogen equilibrium. The attainment of this equilibrium has been interpreted by some authors as signifying normoproteinia, i.e., a normal protein status; and the minimum of protein requirements for nitrogen balance has been equated with the protein requirements of the body. This identification may be justified in the normal individual, where only maintenance is required, but becomes pernicious when applied to the ill. As the body is deprived of adequate protein intake, its protein and caloric needs are correspondingly reduced-as reflected in decreasing azoturia. This has been shown in the professional starvers Levanzin and Succi, and recently confirmed in the dog by Allison. With each day's loss of proteins from the body and further reduction of tissue mass, a lower and lower protein and caloric intake is required to attain equilibrium, so that nitrogen balance reached at such a low plane is more an indication of hypoproteinia than of normoproteinia. In fact, the ease of attaining equilibrium has been suggested as a means of detecting hypoproteinia.

How this misconception may affect clinical practice is illustrated in the shift of attitude in the dietetic regimen in pulmonary tuberculosis. Some three decades ago, a rich diet of eggs, milk, and meats, i.e., a high protein diet, was advised as an important therapeutic measure in this disease. However, in 1926, there appeared a report showing that it took no higher protein intake to achieve nitrogen equilibrium in cases of tuberculosis than in normal persons. This has been interpreted to mean that the protein needs of the tuberculous were no higher than those of the normal person, and an intake of 90 gm. of proteins a day was recommended, with the warning that a higher intake might prove deleterious by provoking increased respiratory activity (because of the specific dynamic action of proteins).

Accordingly, in the most recent authoritative texts on tuberculosis, rich protein feeding is scarcely mentioned, while the possible deleterious effect of increased specific dynamic action has been stressed. While it is true that the maintenance of good protein nutriture is not the only therapeutic measure in tuberculosis, the seriousness of the neglect of this factor, to which such an unbalanced attitude could lead, is well attested by the findings of Chortis concerning the much more rapidly fatal outcome of hypoproteinic tuberculous patients.

Nitrogen equilibrium is only a method of biological bookkeeping and its value is at best circumstantial. Small balances either way are not significant, since the margin of error is high. Accordingly, slow small losses of protein may not be detectable by this method.
Potassium balance has been used as a check on nitrogen balance and so also has weight, but both are subject to several sources of error. Perhaps a better check might be the total body solids as determined by subtracting the total body fluids from the body weight. The gain in total body solids would, however, represent not only protein gains, but corresponding gains in minerals.

From "Review: The Fundamentals of Clinical Proteinology" by Co Tui, M.D., in the *Journal of Clinical Nutrition,* March-April, 1953.

Evaluation of Blood Sugar Tests in Medical Practice

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The following observations are based on a review of glucose tolerance tests and single blood sugar determinations which have been performed on patients in the Carruthers Clinic in the four-year period ending December 31, 1952. Nearly all the patients were ambulatory. All blood sugar estimations were done on venous blood using the Folin-Wu method and a Leitz photoelectric colorimeter.

A total of 685 tests on 617 patients was performed during this period. This survey does not include results of routine blood sugar examinations on diabetic patients under treatment. It is not the policy of our clinic to order blood sugar estimations routinely on each new admission. However, we make every effort to discover early diabetes, and single blood sugar estimations or glucose tolerance tests are performed whenever the history, signs, or symptoms present any suspicion of diabetes.

The various indications for taking the blood sugar tests are listed in Table 1, which also shows the number and percentage of tests taken for each category, and the number and percentage of positive tests under all headings. A rather large group comprising 120 tests had to be defined under the heading "Miscellaneous," representing such conditions as dysuria, polyuria, various endocrine disturbances, brain injuries, poisoning, tiredness, convulsive disorders, dizziness, blindness and various psychoneurotic complaints.

Many tests were performed for several reasons: for example, family history, obesity, and skin lesions. These tests have been allotted to the indication with the highest priority according to the following list: glycosuria, family history of diabetes, skin lesions, paresthesia, miscellaneous, and obesity. Obesity was listed as a cause only when the excess weight was 10 per cent or more over the optimal body weight.

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GLUCOSE TOLERANCE TESTS

The glucose tolerance tests comprised a fasting sample and a sample taken one-half, one, one-and-a-half, and two hours after ingestion of 100 gm. of glucose in solution. The return of the blood sugar to 120 or 130 mg. per 100 cc. two hours after glucose ingestion is now commonly accepted as the significant diagnostic factor. With Duncan[1,2] we have adopted the less strict criterion of 130 mg. The inadequacy of fasting blood sugar determination as a sensitive screening test is brought out by the fact that of 120 abnormal glucose tolerance tests, 83 (69 per cent) showed a fasting blood sugar below 130 mg. While it is well known that mild diabetics may have normal fasting blood sugar, I could find no similar statistical data on this subject in the literature. The objection that these normal readings might be due to self-imposed dietary restrictions just previous to taking the glucose tolerance test can be met by the fact that particular care was taken to instruct patients to follow a diet providing a minimum of 300 gm. of carbohydrate for three days previous to the glucose tolerance tests. No subject had had insulin for at least one week preceding the test, and it was made sure that the patients were free from febrile complications and hyperthyroidism. As initially mentioned, only a few of our patients were hospitalized while their glucose tolerance tests were being made, and none of them could be considered as bedridden. This is important, since Blotner[3] has shown that bed rest results in abnormal blood sugar curves.

Lawrence[5] has coined the term "oxyhyperglycemia" for a condition which is common in cases in which there is rapid emptying of the stomach, especially after gastroenterostomy or partial gastrectomy. After administration of glucose the blood sugar rises rapidly from a normal fasting level to over 200 or even 300 mg. per 100 cc., but returns rapidly to the fasting level in normal time. This curve is not indicative of diabetes mellitus. Eight of our cases fall into this group. Marble[4] believes that one

TABLE 1
Summary of tests for diabetes

Reason for test	Kind of test: Glucose tolerance		Fasting blood sugar		Postprandial blood sugar		Exton-Rose		Modified tolerance		Total tests		Positive tests	
	Total	Abnormal	Total	Abnormal	Total	Abnormal	Total	Abnormal	Total	Abnormal	No.	%	No.	%
Glycosuria	84	44 (52.4%)	103	45 (43.7%)	50	18 (36.0%)	25	14 (56.0%)	6	3 (50.0%)	268	39.1	124	46.3
Family history	81	42 (51.8%)	20	2 (10.0%)	20	7 (35.0%)	14	8 (57.1%)	3	0	138	20.1	59	42.8
Skin lesions	14	7 (50.0%)	13	5 (38.5%)	1	0	2	0	1	0	31	4.5	12	38.7
Paresthesia, neuritis, pruritus	16	7 (43.7%)	15	1 (6.7%)	14	5 (35.7%)	4	3 (75.0%)	0	0	49	7.2	16	32.7
Miscellaneous	31	8 (25.8%)	58	11 (18.9%)	22	6 (27.3%)	6	6 (100.0%)	3	2 (66.7%)	120	17.6	33	27.5
Obesity	18	12 (66.7%)	25	4 (16.0%)	22	8 (36.4%)	8	7 (87.5%)	6	1 (16.7%)	79	11.5	32	40.5
Totals	244	120 (49.2%)	234	68 (29.1%)	129	44 (34.1%)	59	38 (64.4%)	19	6 (31.6%)	685	100.0	276	40.3

cannot disregard the height to which a glucose tolerance curve goes, whereas authorities like Duncan,[1,2] Lawrence,[5] and Mosenthal[6] give little heed to the peak of the curve, provided that the blood sugar returns to 130 mg. or below by the end of two hours. In the 124 glucose tolerance tests which satisfied this requirement and were therefore interpreted as nondiabetic, 51, or 41 per cent, showed a rise in blood sugar over the accepted critical peak level of 170 mg. at some time during the examination. On this basis alone, these tests could have been wrongly interpreted as indicative of diabetes. Adding to these 51 cases the 83 abnormal tests with normal fasting blood sugar, one perceives that 134 of 244 glucose tolerance tests, or 55 per cent, yielded information which could not have been obtained if only a single test had been employed.

FASTING BLOOD SUGAR TESTS

Taking the foregoing observations into consideration, it is not surprising that the percentage of abnormal findings in the fasting blood sugar tests was much lower than in the glucose tolerance tests—29 per cent against 49 per cent.

POSTPRANDIAL BLOOD SUGAR TESTS

Most of the postprandial tests were made after an ordinary meal, and in only a few instances was a special test meal prescribed. These tests were made at various intervals after eating, generally one hour. Any reading over 170 mg. per 100 cc. was considered abnormal, and any reading below 130 mg. was considered normal, regardless of the time interval between the meal and the taking of the sample. The tests between 130 and 170 mg. were reviewed to ascertain the time interval between the meal and the taking of the sample and were assessed accordingly. It is, of course, important that this time relation be known. A reading which may be normal one hour after a meal could be highly abnormal after two hours.

EXTON-ROSE TESTS

The number of Exton-Rose tests performed at this clinic has decreased every year. This test is perhaps more convenient to perform than the standard glucose tolerance test, but its accuracy has been questioned.

MODIFIED TOLERANCE TESTS

Nineteen tests are recorded as modified glucose tolerance tests. They all comprised one fasting and one postprandial blood sugar reading. In six tests this sample was taken forty-five minutes after ingestion of 50 gm. of glucose; in the remaining thirteen the specimen was taken one hour after the ingestion of a meal rich in carbohydrates. The number of these tests performed is, however, too small to be statistically significant.

SUMMARY AND CONCLUSIONS

1. Over 40 per cent of 685 blood sugar tests per-

formed on 617 patients suspected of having diabetes yielded abnormal readings.

2. Abnormal findings numbered 29 per cent of the fasting blood sugar tests, compared with 49 per cent of the glucose tolerance tests.

3. Normal fasting blood sugar levels were found in 69 per cent of cases in which the glucose tolerance test indicated diabetes.

4. Forty-one per cent of otherwise normal glucose tolerance tests reached a peak level of over 170 mg. per 100 cc.

5. Nearly 55 per cent of 244 glucose tolerance tests yielded information which could not have been obtained had a single test been employed.

6. A normal fasting blood sugar is of little value for excluding mild diabetes.

7. If postprandial blood sugar values are employed for diabetic case findings, the time interval between food ingestion and taking of the sample must be noted and the test interpreted accordingly.

8. If only a single test can be employed, it appears that one taken two hours after the ingestion of 100 gm. of glucose has the highest selectivity. Failing this, a postprandial test is of greater diagnostic value than a fasting blood sugar reading.

9. These studies demonstrate the necessity of integrating the laboratory findings with the clinical picture.

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Antivivisection Activities

Antivivisectionists, and American Humane Association strategists lined up with them, appeared rudely shocked by the recent move of the Washington, D. C., Commissioners to provide a means for selling the District's condemned pound animals for use in research and teaching. The enemies of medical progress had been boasting all year about having stopped three pound-bills in state legislatures and admitted that they were totally unprepared for the D. C. action. The inside story of the development in Washington is this: With the opening of Congress last year, an attempt was made by Rep. Auchincloss in New Jersey to turn the D. C. municipal pound over to a private animal welfare group with a law disguised to look like an economy measure. In the ensuing uproar from medical scientists all over the country, it was divulged that the D. C. pound annually showed a profit of over $50,000 and that 6,000 animals were killed there every year that could be used for research if Poundmaster Marks, an old antivivisectionist, would release them. Local scientific and political leaders of the District then took a hand in working out the present arrangement which was incorporated in the D. C. reorganization plan. Latest development at this writing was the hearing on January 25 at which antivivisectionists presented 53 witnesses, ranging from testimony that there was no such disease as rabies to solemn assurance by Dr. Hoxey that he had found cure for cancer without animal experimentation. Antivivisectionists, as in all campaigns, wrote letters furiously from all parts of the country. The total, however, was only 12,000, indicating a serious drop in antivivisectionist strength throughout the nation.

If the Washington arrangement goes through, and it appears likely, it will mark the second substantial victory for medical research proponents in the still-young year. A series of amendments to the Illinois pound law went into effect on the first of this year, giving force to that measure. They had been passed through both houses of the Illinois legislature at its last session without a single dissenting vote. Principal amendment is the one which places humane societies with pound contracts in the same status with regard to the law as municipal pounds.

From an editorial in the *Bulletin for Medical Research,* Jan.-Feb. 1954.

Fetal Mortality in Diabetic Pregnancies*

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The fetal mortality in pregnancies of diabetic women is still high, and there is some disagreement as to the best treatment. One of the points in dispute is the value of hormone therapy during pregnancy. White[1,2] has reported a fetal mortality which is among the lowest obtained so far. She ascribes this success to the administration of stilbestrol and progesterone during pregnancy, but this explanation is not generally accepted. As stated, for example, by Brandstrup and Okkels,[3] it would be valuable to elucidate the role of the control of the diabetes and the maternal hyperglycemia. This applies not only to the infant mortality, but also to the size, weight, water content, etc., of the infants and their subsequent fate, particularly with regard to the incidence of diabetes.

As part of the investigations which are being carried out in Lying-in Department B, Rigshospitalet, on problems pertaining to diabetes and pregnancy, it was planned late in 1945 to study these factors by an intensive classical treatment of the diabetes and by conservative obstetrical management, carried out by a small number of doctors. In this paper the fetal mortality will be reported.

LONG-TERM AND SHORT-TERM TREATMENT

The material summarized in Table 1 comprises all deliveries by diabetics in Lying-in Department B during the eight-year period 1946-1953. The weight limit was fixed at 1 kg. There were 161 mothers who gave birth to 192 infants in 189 deliveries. There were three twin births and the highest number of deliveries by any patient was three.

The material is divided into two groups according to the stage of pregnancy at which the patient first applied to the clinic. This occurs at very different stages, since the Department receives all kinds of obstetrical complications without selection and many emergency cases. A few diabetics attend from the very first months of pregnancy, while others are not seen until they are in labor. The majority, however, are seen toward the end of pregnancy. All those who were seen at a minimum of 53 days before the calculated term were classified as having long-term treatment; those who were not seen until later were considered to have had short-term treatment.

Patients who, according to the time of their first application, were designated as long-term cases were transferred to the short-term category if they were in coma, precoma or in labor, or had been delivered when first seen. The short-term classification was also applied in cases of fetal death or delivery within eight days after the first application (Table 2).

The skew value of 53 days was obtained as follows. In a previous study[4] of the infants' blood sugar, patients

TABLE 1

Summary of Material

	Long-term treatment	Short-term treatment	Totals
Mothers	73	102	161*
Deliveries	78	111	189
Babies	80	112	192

*14 patients are included in both the long-term and the short-term groups.

TABLE 2

Patients seen for the first time 53 days or more before the calculated term, but transferred to the short-term group

Cause of Transfer	Number of Infants	
	Total	With birth weight of 2.5 kg. or over
Coma or precoma, or in labor at first attendance	8	3
Delivery or death of infant within 8 days after first attendance	12	2
Totals	20	5

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who had been in the Department for a continuous period of at least 32 days prior to delivery were designated long-term patients. Since delivery takes place on the average three weeks before the calculated term, the first application has been a minimum of 53 days before the calculated term. The 53 days are maintained as a limit, but the need for 32 days' stay in the Department prior to delivery is not included in the definition here, since in that case the long-term patients would be selected, including too many patients without complications indicating interruption. In a study of the value of a therapeutic method, it is assumed that all patients of the treated group have received some treatment. Therefore, it was necessary to make the above exception. As evident from Table 2, most infants weighed less than 2.5 kg.

The criteria for long-term patients are highly unfavorable for the therapeutic results in this group. That is to say, all deaths among the infants whose mothers applied to the clinic a minimum of 53 days before their calculated term are allotted to the long-term group after only eight days' treatment of the mothers, whether they have been outpatients or inpatients. Of course, what is important is that on the average the long-term patients have been treated for a much longer time than the short-term patients, as is apparent from Table 3. All the long-term patients and 14 per cent of the short-term patients were seen for the first time 53 days or more before the calculated term, and 78 per cent of long-term and 10 per cent of short-term patients had had a continuous hospital stay of 30 days or longer immediately before delivery. Fourteen patients are included in both the long-term and the short-term groups.

ROUTINE EXAMINATIONS

All the patients were examined by ophthalmologists for diabetic retinopathy and cataract and by X ray for calcified arteries of the arms and legs. In addition, frequent examinations were made for urinary tract infections, and daily examinations were made for proteinuria and hypertension. No search for calcification of pelvic arteries could be made during pregnancy, and in fact only one case with this condition was known.

TREATMENT

All cases were treated in the same way, but for varying periods of time, as indicated. The aim was to keep the blood sugar as near the physiological level as possible, to prevent acidosis and insulin reactions, and to prevent and combat toxemia and edema. In brief, the treatment was as follows. The diet contained 1800 to 2000 calories, 80 to 90 gm. of protein, 175 to 200 gm. of carbohydrate, and about 80 gm. of fat. In addition, a supplement of vitamins, calcium, and iron was given.

In an effort to keep the blood sugar low, four daily blood sugar determinations were made on inpatients. The extent to which this aim was attained is exemplified by the fact that in the first 18 long-term mothers the pregnancy level of the blood sugar (average of the four daily determinations during the last continuous stay in hospital, average 52 days) ranged from 108 to 167 mg. per 100 cc., and the common average level was 133 mg. Adequate doses of insulin were used, preferably crystalline protamine insulin (NPH insulin) plus regular insulin administered simultaneously twice daily. The average daily dose of insulin for all inpatients was about 70 international units (for details see Pedersen[4]).

Restriction of table salt and fluid to combat toxemia and edema was frequently prescribed. Abdominal amniotomy was tried in two cases. No hormones, mercurial preparations, ammonium chloride, rutin, or similar substances were used.

The schedule for visits and control was as follows: during the first months ambulatory control about every three weeks, and from the beginning of the fifth month every week. About eight weeks before the calculated

TABLE 3

Days before calculated term (first attendance) or delivery (continuous stay)

Diabetic group	Number of Days										
	0—9	10—19	20—29	30—39	40—52	53—59	60—69	70—79	80—89	90+	Totals
First attendance:											
Short-term	3	2	14	32	40	2	6	3	3	2	107*
Long-term	0	0	0	0	0	21	16	10	10	21	78
Continuous stay:											
Short-term	41	31	28	8	2	1	0	0	0	0	111
Long-term	7	4	7	21	21	12	3	1	1	1	78

*No data available in 4 cases.

term the patient was hospitalized for prophylactic purposes and remained in the Department until delivery, which was usually induced about three weeks before term. This applied to uncomplicated cases. Complications which did not yield at once to ambulatory measures called for immediate hospitalization. In the presence of complications, delivery sometimes had to be induced before the 38th week.

As seen from Table 3, only a few of the long-term patients had been controlled throughout the pregnancy. The remainder were seen for the first time at a number of different stages of the pregnancy, and the short-term cases arrived so late that they were only inpatients. Before coming to the clinic the patients had been controlled at various medical outpatient or inpatient departments in Copenhagen. During the past few years, many have come from the Steno Memorial Hospital and the Hvidøre Hospital (private hospitals for diabetics). Some come from provincial hospitals, others from general practitioners, and some had no control at all. Moreover, some patients had attended the outpatient antenatal clinic of Rigshospitalet before coming to us. It must be borne in mind that the material is unselected, all kinds of patients coming at all periods of pregnancy, many as emergency cases.

The obstetrical management was conservative, but was conducted in the same manner in long-term and in short-term cases. Nearly all deliveries were induced—by drugs and/or rupture of the membranes—about the 38th week. Only 16 cesarean sections were performed (8 per cent), whereas forceps deliveries were common. It is planned to give details of the obstetrical management in a later paper.

After suction of the hypopharynx, all the newborn babies were placed in incubators and given oxygen, warmth, and humidity routinely for the first 24 hours. During this period all the babies were fasted (*cf.* Pedersen[5]).

The ambulatory control of the long-term patients was performed by the author, who received the advice of the obstetricians when necessary. All inpatients were treated daily by me, and the obstetrical management was conducted by a small number of obstetricians under the supervision of Prof. Brandstrup. A pediatrician was called whenever needed.

CLINICAL FEATURES

From Table 4 it will be seen that the frequency of severe diabetes was 63 per cent, of diabetic retinitis 23 per cent, and of calcified arteries 5 per cent; 44 per cent of the patients were primiparas. On the whole, the long-term and short-term series do not exhibit differences sufficiently marked to account for the difference found in fetal mortality, especially for infants with a birth weight of 2.5 kg. or over. The incidence of toxemia (unclassified) was 30 per cent, which agrees with other series of unselected cases (Jones[6]). The frequency of hydramnion was 50 per cent (more than 1000 ml.) or 20 per cent (more than 1500 ml.) (Pedersen and Jørgensen[7]).

CLASSIFICATION

An entirely satisfactory classification of pregnant diabetics remains to be found. This is also Oakley's[8] opinion. This is not only because we do not yet know all the causes of the high fetal mortality, but because

TABLE 4

Comparison of long-term and short-term series

	Onset of Diabetes: Age 12 Years or Less		Onset of Diabetes: Age 21 Years or Less		Duration of Diabetes 15 Years or More		Diabetic Retinitis (and cataract)		Proliferative Retinitis	Calcification of Leg (or Pelvic) Arteries		Diabetic Nephropathy*		White's Classification Groups† C+D+F		White's Classification Groups† D+F		Congenital Malformations: Total		Congenital Malformations: Major	Primiparas		Cesarean Section	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	NO.	%	NO.	%
Long-term	15	19	45	58	15	19	20	26	2	6	8	22	28	51	65	26	33	4	5	1	29	37	13	17
Short-term	28	25	73	66	22	20	23	21	1	4	4	24	22	69	62	35	32	9	8	5‡	54	49	3	3
Totals	43	23	118	62	37	20	43	23	3	10	5	46	24	120	63	61	32	13	7	6	83	44	16	8

*In most cases varying degrees of pyelonephritis.
†The number of cases belonging to group E cannot be stated.
‡Four deaths, birth weight less than 2.5 kg.

treatment may mask the natural course of the disease.

Thus, in this series the fetal mortality is only slightly increased for primiparas (primiparas 32 per cent, multiparas 23 per cent). It increases with increasing duration of diabetes (0-9 years, 23 per cent; 10-19 years, 30 per cent; 20 years or over, 45 per cent; and in the presence of diabetic retinopathy, 42 per cent). There is, on the other hand, no correlation with the age of onset of the diabetes (1-15 years, 31 per cent; 16-24 years, 19 per cent; 25 years or over, 30 per cent, which was found to be marked in a previous study (Pedersen[9]). There was, moreover, no convincing correlation with calcified peripheral arteries or the severity of retinitis. However, a larger group with a high mortality may be set up. This group should, on the basis of the present study, include the following conditions: diabetic retinopathy, cataract, calcified arteries, vascular nephropathy, or diabetes of more than twenty years' standing.

It will be seen that this group does not differ essentially from groups D, E, and F in White's[1] classification. This classification suffers from the practical disadvantage that an accurate classification into groups E and F presupposes fairly extensive knowledge of vascular complications before the patients become pregnant. Group F, vascular nephritis, includes constant albuminuria before the pregnancy, but not pyelonephritis with varying pyuria and intermittent albuminuria (White[10]). In our series, the number of cases belonging to group E cannot be stated, and the numbers in group F will be a minimum. However, for the time being I shall use White's classification, omitting group E.

It is suggested that the mortality for infants weighing 2.5 kg. or more should always be reported. The reasons are, among others, that the indication for therapeutic interruption before this weight has been attained may be lacking in uniformity, that a number of clinics supervise the patients only during the latter part of pregnancy, and that differences in fetal mortality due to major congenital malformations will decrease.

RESULTS AND DISCUSSION

The results of the treatment are given in Table 5. The mortality in the total material, 26 per cent, corresponds to that reported, for example, by Jones[6] and to Oakley's[8] series (King's College Hospital, London). The total mortality in our maternity hospital in previous years (1926-1945) was 38 per cent. Thus there is a definite, though not a large, gain.

It will be seen that the mortality in the long-term cases is 11 and 9 per cent, but 36 and 25 per cent in the short-term cases, for birth weights of 1 and 2.5 kg. and over respectively. In either case the difference is statistically significant.

TABLE 5

Fetal mortality in long-term and short-term cases

	Birth weight 1 kg. or over			Birth weight 2.5 kg. or over		
	No. of Babies	Fetal loss		No. of Babies	Fetal loss	
		No.	%		No.	%
Long-term	80	9	11	70	6	9
Short-term	112	41	36	92	23	25
Totals	192	50	26	162	29	18

In Table 6 the material is classified according to White.[1] Groups A and F are small, and as stated above, the number in F are a minimum. In the total series there is no increase in mortality from group B to C, and it is noteworthy that in our long-term series the mortality for groups A, B, C, and D is 8 per cent, with no increase between groups B, C, and D. It would appear most practical to combine groups A, B, and C into one group and D and F into another. As is apparent from Table 7, the mortality now increases from groups A, B, and C to groups D and F for both long-term and short-term cases. The long-term series exhibits a lower mortality in both groups, and the result is not altered by paying attention only to birth weights of 2.5 kg. or over.

Tables 5 and 7 show that 20 infants (18 per cent) in the short-term series weighed less than 2.5 kg. and that 18 of them died. In the long-term series there were 10 infants (13 per cent) with birth weights of less than 2.5 kg., including two pairs of twins. Only 3 of these died.

It was previously shown (Table 4) that the long-term and short-term series are comparable. In our opinion, the prolonged treatment in the long-term series is without doubt the cause of the lower mortality. Indeed, it is not surprising that the result may be improved by intensive treatment and supervision carried out by a few doctors.

The mortality in the long-term series, 11 per cent (Table 5), corresponds to that reported by Reis[11] and by Pease.[12] Neither of these series, however, contained as many cases of severe diabetes as the present one. The mortality in the long-term series is also as low as in the series of White[1] and Nelson.[13] Table 8 sets out some differences and similarities between the long-term series and the series of Nelson. The latter contained only a few more severe diabetics (72 per cent) than ours (65 per cent).

TABLE 6

Fetal mortality classified according to White[10]
(Class E omitted)

Diabetic Group	Group A Glucose-tolerance test diabetes (no insulin).	Group B Diabetes: onset 20+ yr. Duration 0-9 yr. No Vascular disease.	Group C Diabetes: onset 10-19 yr., duration 10-19 yr. No Vascular disease.	Group D Diabetes: onset less than 10 yr., duration 20 yr. or more. Calcified arteries in legs. Diabetic retinopathy.	Group F* Vascular nephritis
Long-term:					
No. of infants	1	28	25	21	5
Fetal loss	0	2	3	1	3
Short-term:					
No. of infants	5	38	34	32	3
Fetal loss	0	17	6	17	1
All cases:					
No. of infants	6	66	59	53	8
Fetal loss	0	19(29%)	9(15%)	18(34%)	4(50%)

*Minimum figures (*cf.* text).

TABLE 7

Fetal mortality in relation to White's Classification and birth weight

	White's Classification Groups (E not stated) A+B+C				D+F			
	No. of Babies	Fetal loss No.	%		No. of Babies	Fetal loss No.	%	
Birth weight 1 kg. or over:								
Long-term	54	5	9	21	26	4	15	36
Short-term	77	23	30		35	18	51	
Birth weight 2.5 kg. or over:								
Long-term	50	4	8	13	20	2	10	29
Short-term	64	11	17		28	12	43	

Our material shows that without sex endocrine therapy and without extensive use of cesarean section, it is possible to obtain results which are as good as those of White in groups A, B, C, and D. As regards groups A and B, this is also evident from Reis's[11] series. Our series is still too small to assess the mortality for group F, but this seems to be the only group in which the mortality will exceed 10 per cent.

We intend to continue in the same way without administration of hormones. When the series has become larger, we shall analyse the long-term and short-term groups to find out which mortality-increasing factors our treatment has diminished and which it has failed to affect.

TABLE 8

Comparison of this series with that of Nelson, Gillespie, and White[13]*

	Fetal mortality	Severe diabetics. White's groups C+D+E+F	Primiparas	Cesarean section	Rutin, mercuhydrin, ammonium chloride	Hormone treatment
White's series	10%	72%	Nearly 50%	70%	+	+
This series (long-term)	11%	65%	37%	17%	None	None

*In both series the following conditions existed: close individual supervision and management by a few doctors; best possible chemical control of diabetes; restriction of salt (and fluid); early timing of delivery; suction, incubation, and fasting of infants.

SUMMARY

Lying-in Department B, Rigshospitalet, Copenhagen, is a large Department receiving, without any selection, patients with complications as well as many emergency cases.

During the years 1946-1953 a total of 189 diabetic pregnancies were observed and 192 babies were born (birth weight 1 kg. or over). The fetal mortality was 26 per cent.

This material is divided into two groups: long-term treated and short-term treated cases, according to the stage of pregnancy at which the patient was first seen. The long-term cases were treated for a much longer time during the latter part of pregnancy than the short-term cases. Both groups received the same treatment, conducted by the same few individuals, and consisting of intensive classical management of the diabetes by diet and ample insulin and conservative obstetrical management. Cesarean section was used in only 8 per cent of the cases. No hormones were administered. All the infants were fasted for 24 hours. The rate of severe diabetics (Groups C, D, E, and F according to White) was 64 per cent, of diabetic retinitis 23 per cent, of calcified arteries 5 per cent, and of primiparas 44 per cent—without any differences between the long-term and short-term series.

In 111 short-term pregnancies (112 babies) the fetal mortality was 36 per cent; in 78 long-term cases (80 babies), it was 11 per cent. In the long-term series the fetal mortality in the White groups A, B, C, D, and F was 0, 7, 12, 5, and 60 per cent, respectively.

In view of the results obtained in the long-term series, we have not felt inclined to try sex endocrine treatment, but shall continue to collect a larger series of long-term patients, especially in the White group F.

While awaiting a more perfect classification, the author suggests a classification according to White (omitting class E) supplemented by separate statements on the fetal mortality for birth weights of 2.5 kg. and over.

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Effect of Cortisone on Carbohydrate Metabolism Measured by the "Glucose Assimilation Coefficient"

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It is generally held that, except for changes in insulin activity, the usual clinical doses of cortisone have but slight effect on the carbohydrate metabolism of normal subjects.[1-4] Among the hundreds of patients treated with cortisone, only a very small number have shown diabetes, usually of transient nature.[5]

By mathematical analysis of intravenous glucose tolerance tests, it is possible to calculate a "glucose assimilation coefficient"[6] and to detect thereby changes in carbohydrate metabolism, which are brought about by cortisone and which escaped other methods of investigation. (In studying cases of mild diabetes in which intravenous glucose tolerance tests were made together with fractionated glycosuria estimations, it has been shown that when the fasting blood sugar level lies between 100 and 150 mg. per 100 cc., by the Shaffer-Hartman method, the greatest part of the glycosuria occurs during the first 15 minutes of the test. Since our first sample was taken at 15 minutes, the curve measures only glucose assimilation. In diabetes, with the fasting blood sugar reaching the renal threshold, the curve is influenced by tissue assimilation and also by renal leakage.)

METHOD

When glucose is injected rapidly into the veins, the blood sugar rises abruptly and reaches a peak within the first 5 minutes. Afterwards it falls, at first sharply, then at a more gradual rate. In normal subjects the glycemia usually reaches its previous value between 45 and 120 minutes. Sometimes, there is a hypoglycemic phase, followed by some slight oscillations.

The first part of the intravenous glucose tolerance test (Figure 1) corresponds to the diffusion of the injected glucose into the blood and the extracellular fluids. The terminal part reflects the action of secondary adaptation mechanisms.

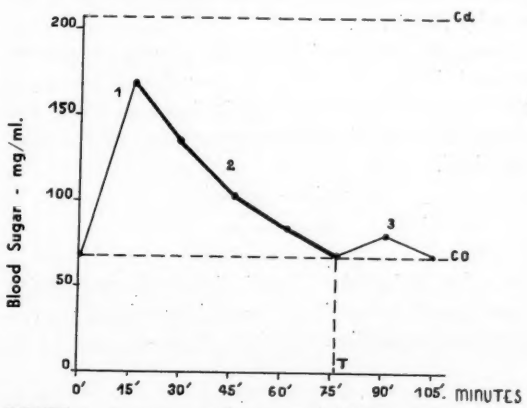

FIGURE 1. Intravenous tolerance test. Mean values.

As to the middle part of the curve, it has been shown by previous work from this laboratory using measurements of the extracellular fluids, that it corresponds to the removal of blood glucose by the tissues and that this process follows an exponential law.

When the logarithms of the blood glucose values, obtained between 15 and 60 minutes, are plotted on semilogarithmic paper they fall exactly on a straight line (Figure 2).

If this line is extended to the time 0, it yields the same value of theoretical blood glucose, as can be calculated by adding to the fasting blood glucose the quantity of injected sugar, divided by the volume of extracellular fluids. This means that the diffusion of

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Presented at the joint meeting of the American Diabetes Association and The Endocrine Society in New York on May 30, 1953.

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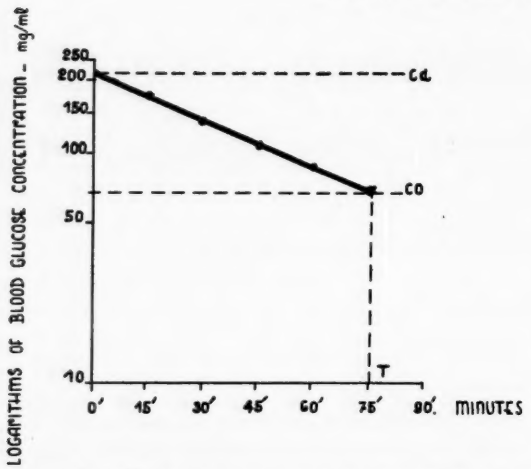

FIGURE 2. Intravenous tolerance test. Semilogarithmic graph of mean values.

the injected glucose is almost instantaneous and thus that after 15 minutes, the disappearance rate of the glucose from the blood is only dependent on its uptake by the tissues.

From the mathematical formula of this exponential curve, it is easy to calculate a factor K, which indicates the slope of the semilogarithmic line, and which thus measures the speed of the glucose disappearance from the blood.

$$K = \frac{\log_{10} C - \log_{10} C'}{t' - t} \cdot 2.3$$

In a first series of 20 hospitalized patients suffering from miscellaneous diseases but without detectable carbohydrate metabolism disorders, the mean value for K, calculated per cent, has been : 1.55 ± 0.31.

Calculation of the factor K on data published by Lozner and coworkers[7] and concerning young and healthy subjects has yielded the value: 1.96. In a group of mild diabetics the value obtained was 0.5.

RESULTS

The changes of the glucose assimilation have been studied in 18 patients submitted to cortisone treatment for rheumatoid arthritis, asthma or periarteritis. These patients were in satisfactory nutritional condition. During the investigation they were maintained on a fairly constant diet.

The values of intravenous glucose tolerance tests are given in Table 1. Statistical analysis (Table 2) using the Student-Fisher test and the pairing system indicates that except for the difference between previous values and values observed after 3 gm., the observed changes (Figure 3) are significant.

COMMENTS

Besides some reduction in insulin activity, the usual tests fail to detect any significant change in carbohydrate metabolism of normal subjects submitted to therapeutic doses of cortisone.

The calculation of the "glucose assimilation coefficient" provides a means for detecting and measuring slight changes in the glucose tolerance. The physiological and mathematical basis of this test has been analyzed in previous work.[6] Application of this method to the study of patients submitted to cortisone treatment indicates appreciable alterations in their glucose tolerance, which are dependent on the duration of the treatment.

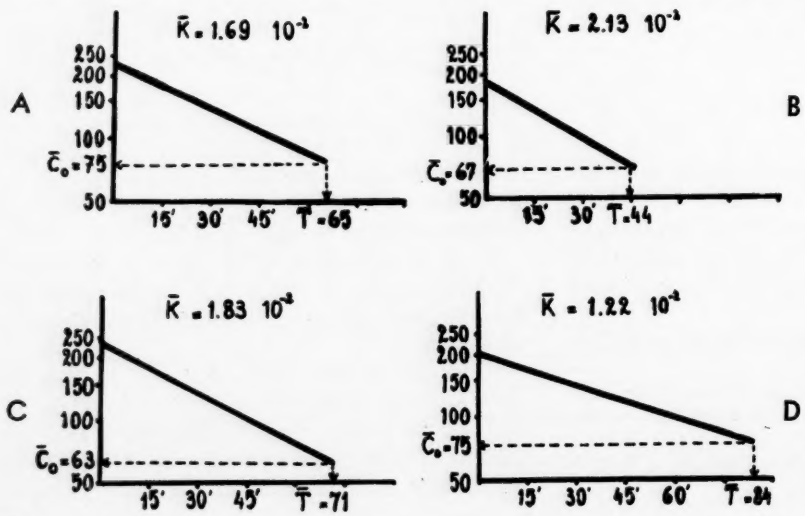

FIGURE 3. Effects of cortisone treatment on glucose tolerance (semilogarithmic lines). A. Before cortisone treatment. B. After 7 days of treatment. C. After 21 days of treatment. D. After protracted treatment.

TABLE 1

Values of blood glucose during intravenous glucose tolerance test (mg. per 100 ml.) (1) before, (2) after 1 gm., (3) after 3 gm. and (4) after 10 or more gm. of cortisone administration

Cases	1. Before Cortisone						2. After 1 gm. Cortisone						3. After 3 gm. Cortisone						4. After 10 gm. Cortisone					
	0′	15′	30′	45′	60′	75′	0′	15′	30′	45′	60′	75′	0′	15′	30′	45′	60′	75′	0′	15′	30′	45′	60′	75′
	mg. per 100 ml.						mg. per 100 ml.						mg. per 100 ml.						mg. per 100 ml.					
1	60	120	97	81	65	55	56	133	114	98	—	68	68	124	103	82	63	(60)	56	140	97	68	(63)	(60)
2	62	133	115	96	92	75							70	112	87	85	64	(71)	61	146	101	83	(80)	(69)
3	51	165	132	106	89	—	81	169	148	121	108	83	79	185	136	112	92	75						
4	50	148	—	84	—	54	66	—	149	135	118	96	73	174	132	114	93	86						
5	55	154	119	96	72	60													64	100	72	(62)	(66)	(62)
6	46	121	92	77	—	51													60	111	90	66	(81)	(66)
7	87	204	170	152	135	113	75	187	162	135	110	(124)	89	—	164	144	113	104						
8	93	211	154	131	109	—	85	214	171	152	126	108	92	190	163	133	118	111						
9	68	160	127	102	(95)	(77)	60	128	100	86	66	(68)	62	146	116	—	75	63	68	219	179	143	113	—
10	60	149	113	82	(80)	(72)	75	132	111	90	—	81	61	—	106	—	—	—	113	190	124	96	(94)	(81)
11	46	130	86	58	(51)	—	75	160	—	102	83	68	70	186	150	115	95	81	63	190	132	94	64	(70)
12	60	158	86	64	—	—							81	209	142	100	(88)	(70)						
13	78	224	160	130	(120)	—	90	161	145	128	110	101												
14	67	174	118	102	72	60													66	169	130	80	(77)	(60)
15	59	157	124	102	89	—	93	152	135	130	113	—												
16	50	140	84	65	—	—	69	171	—	90	—	58												
17	97	203	160	—	95	—	58						72	—	121	99	72	—						
18	50	110	67	41	(39)	(43)	73	167	118	101	72	(83)	68	148	94	(85)	(69)	(65)	62	169	116	—	53	(59)

K factors calculated from above data. Mean$\pm$SE$_m$ (Standard error of the mean)

1.84 ± 0.16	1.22 ± 0.11	1.69 ± 0.17	2.13 ± 0.11

TABLE 2

Study of the significance between mean differences by the use of the Student-Fisher "t" test and pairing

$$t = \frac{|\bar{x}|}{\frac{\text{S.D.}}{\sqrt{N}}}$$

$\bar{x}$ = mean value of individual differences between glucose assimilation coefficients
S.D. = standard deviation of the difference
N = number of individuals treated in each group
P = value of probability

Treatment	N	$\bar{x}$	S.D.	t	P
Before cortisone—after 1 gm.	12	1.84 — 1.22 = 0.62	0.44	4.88	0.01>P
Before cortisone—after 3 gm.	11	1.83 — 1.69 = 0.15	0.58	0.83	P>0.1
Before cortisone—after 10 gm.	9	1.83 — 2.13 = 0.30	0.54	1.87	0.1>P>0.05
After 1 gm.—after 3 gm.	8	1.29 — 1.54 = 0.28	0.35	2.25	0.1>P>0.05
After 1 gm.—after 10 gm.	5	1.46 — 2.14 = 0.68	0.35	4.43	0.02>P>0.01

After one week, the glucose assimilation is markedly inhibited. At the third week of treatment, however, there is a return to the normal value and after several weeks the glucose uptake is even better than before treatment. These changes can be considered differently according to the theory which is admitted concerning the action of cortisone on carbohydrate metabolism: either the theory of inhibition of glucose utilization or that of neoglucogenesis. Recent work of Stetten and coworkers[8] seems to indicate that cortisone acts by both mechanisms.

In the normal subject, the test used in this work certainly indicates the rate of glucose assimilation. Even if according to Levine,[9] cortisone administration induces marked gluconeogenesis, the disappearance of the extra glucose from the blood cannot be accounted for except by admitting that the glucose has finally passed from the extracellular fluids into the cells.

Thus, admittedly the changes in the "glucose assimilation coefficient" do not give information on the intimate mechanism of this underlying process. Nevertheless they measure alterations in the glucose uptake

by the tissues.

It may be of interest to note that similar changes have been observed in the insulin activity tested in 10 of the patients.[10] At the time of reduced glucose assimilation the insulin activity is also diminished; during protracted treatment increased glucose uptake is found together with enhanced insulin activity.

These observations suggest that usual therapeutic doses of cortisone induce definite but transitory alterations in the carbohydrate metabolism, together with changes in insulin activity. This would be in agreement with recent work (Drury and others,[12] Bouckaert and deDuve,[11] Levine,[9]) concerning the action of insulin as chiefly concerned with the assimilation of glucose by the tissues.

The observations showing improvement of carbohydrate tolerance and of insulin activity under protracted treatment might be explained either by reduction of the endogenous steroid secretion or by increased insulin activity. Whatever the explanation be, these observations further stress the importance of the physiological reactions of the subject who is treated with a diabetogenic steroid.

SUMMARY

In 18 patients with miscellaneous diseases, submitted to cortisone treatment, the glucose tolerance has been measured by the "glucose assimilation coefficient." Definite changes have been observed, showing reduction of tolerance in the initial stages of cortisone administration, improvement under protracted treatment.

ADDENDUM

Since the presentation of this paper (May 30, 1953), 15 additional cases have been studied. It has been found that with the use of smaller doses of cortisone, the inhibiting effect of the drug on glucose assimilation is of very short duration. After 10 days of therapy the glucose assimilation coefficient may begin to increase.

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DISCUSSION

BENJAMIN JABLONS, M.D., (*New York, N. Y.*): We have been studying sugar tolerance tests in cases of rheumatoid arthritis and other conditions treated with ACTH. We have found, in common with others, three types of response.

In one group apparently normal physiologically, ACTH does not modify the sugar tolerance test. In another group, ACTH produces a definite change from a normal sugar tolerance curve to a diabetic sugar tolerance curve. In a third group, including cases in which there may be latent diabetes, or fully developed diabetes, the diabetic state becomes considerably aggravated after ACTH administration and the sugar tolerance curve becomes considerably worse.

This is apparently in keeping with the conclusions of Dr. Bastenie, that the physiologic status of the individual

determines, to a large extent, how the adrenal steroids act in regard to diabetogenesis.

E. H. RYNEARSON, M.D., (*Rochester, Minn.*): I am sure I am speaking on behalf of the American Diabetes Association in thanking Dr. Bastenie for this splendid talk. I am equally sure that most of us in this room are aware that in too many instances cortisone is being used even before aspirin! It is being used rather indiscriminately in an effort to bring relief to patients with indeterminate diagnoses. We are almost certain to see more disturbances of carbohydrate metabolism in patients so treated and the work of Dr. Bastenie and his associates should prove helpful in our understanding of this enlarging problem.

When Dr. Bastenie closes his discussion, I would be interested to ask whether he has made observations of the glucose assimilation coefficient in patients who have Addison's disease and whether he has found any marked changes in cases of Cushing's syndrome.

P. A. BASTENIE, M.D., (*Brussels*): We made these observations after several attempts to find a method which would enable us to know exactly if therapeutic doses of cortisone affected the carbohydrate metabolism. We found that the usual oral glucose test, the intravenous tolerance test and even repeated tests do not give good results. We felt that perhaps this test might be a more accurate tool.

We have had the opportunity to study this factor in one case of Addison's disease and found it highly increased, but we had no experience with Cushing's disease. When desoxycorticosterone is given, the fluids are increased: the administered glucose is diffused in a wider "glucose-space" but the glucose assimilation remains unchanged.

Fortified Foods

In the 1930's certain nutritional deficiencies were found to be prevalent in the United States. Alert food processors began adding synthetic vitamins to their products, but with little or no scientific guidance. In 1940 the Food and Nutrition Board of the National Research Council was organized. This board and the older Council on Foods and Nutrition of the American Medical Association have issued statements regarding the addition of specific nutrients to foods from time to time. In November 1953, they reconsidered past statements and issued a joint statement that, although in no way a directive, should serve as a valuable guide.

The report endorses in principle the addition of specific nutrients to certain staple foods provided (1) there is a clear indication that probable advantage will result from such an addition, (2) the food item concerned is an effective vehicle of distribution for the additive, and (3) such addition would not interfere with the achievement of a diet good in other respects. The report further stresses the desirability of meeting the nutritional needs of the people by the use of natural foods insofar as possible. It recommends that foods chosen as vehicles for the distribution of additives should be, when practicable, those that have lost nutrients through refining or other processing. It approves the addition of greater than natural levels of nutrients to foods that are suitable vehicles of distribution when other methods for affecting the desired distribution appear to be less practicable. It recommends considering the restoration of essential nutrients should future technological and economic developments lead to extensive reduction in the consumption of some staple articles of diets. The report approves the enrichment of flour, bread, degerminated corn meal, and corn grits with thiamine, riboflavin, and niacin; the nutritive improvement of whole grain corn meal and white rice; the retention or restoration of thiamine, niacin, and iron in processed food cereals; and the addition of vitamin D to milk, vitamin A to butter and margarine, and iodine to table salt.

It is necessary to set definite limits to the addition of nutrients to food products in order to protect the public from combinations that are irrational or even harmful. Most states have based their laws on the recommendations of the Food and Nutrition Board and the Council on Food and Nutrition. There is good evidence that the policies recommended have benefited the public and have encouraged sound nutritional practices.

From the editorial section
of *The Journal of the*
American Medical Association,
May 8, 1954.

The Type of Diabetes Mellitus Associated with Diabetic Retinitis

George W. Dana, M.D., Baltimore

A remarkable reduction in insulin requirement was observed in the case of an adult woman with diabetes; after requiring 80 units of insulin daily, she later managed without insulin and had normal blood sugar tests. The dominant clinical feature in later years was renal insufficiency. At autopsy, extensive renal changes of the Kimmelstiel-Wilson type were found.

Because of the apparent relation of the amelioration of the diabetes to the development of renal disease in this case, the incidence of renal changes and the severity of the diabetic state were studied in 190 cases of diabetes mellitus autopsied in recent years. These cases were divided into three groups: those with no renal disease, those with renal disease other than the Kimmelstiel-Wilson type and those with the Kimmelstiel-Wilson renal lesions.

The criterion used for the Kimmelstiel lesion was solely the lumpy loop or hyaline mass in the glomerulus. There were 57 patients with the lesion—an incidence of one-third of the diabetic study group. The duration of the diabetes did not differ from that in the two other groups. In general, the patients with the lesion were obese, became hypertensive, developed refractory edema, died in uremia. Their kidneys characteristically showed marked arteriolarsclerosis and arteriosclerosis.

In 60 per cent of the diabetics with the Kimmelstiel lesion, the amount of insulin required progressively decreased as time went on. In a few cases, the diminution of the insulin requirement was so marked that diabetics previously requiring large amounts of insulin became hypoglycemic during treatment with small doses. This illustrates the need for caution. The tendency to amelioration appeared late in the course of the diabetic disease.

From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

Abridgment of paper presented at the Annual Meeting of the American Diabetes Association, New York, May 31, 1953.

Another unexpected finding in the cases with the Kimmelstiel-Wilson renal changes was a striking rarity of acidosis throughout the course of their diabetes, in contrast to its common and repeated occurrence among the controls. Both groups, however, had experienced equivalent stress ordinarily sufficient to cause acidosis, such as infection, gangrene and insulin withdrawal.

In 90 per cent of cases with the glomerular nodules, extensive retinal aneurysms were observed either ophthalmoscopically or by flat plate preparation of the retina at autopsy. These retinal changes were observed in only 10 per cent of the controls.

The statistical data suggest that retinal aneurysms are an intrinsic part of the same entity as the Kimmelstiel-Wilson lesion, an impression in accord with the contemporary studies of Friedenwald, Ashton and others. It was of additional interest in this regard, that 11 of the patients with the Kimmelstiel kidney lesions showed not only the characteristic glomerular nodular massing but neighboring associated aneurysmal dilatations of various other glomeruli, filled with red blood cells and beginning to hyalinize. Such may be the anatomical precursor of the glomerular nodule, and the finding implies a common pathogenesis for the changes in the retinal and renal capillaries.

CONCLUSION

It can be concluded that adult patients with diabetes mellitus who ultimately have Kimmelstiel-Wilson renal damage also develop typical diabetic retinitis, and that the diabetic state often tends to become milder and that it is characterized by a rarity of acidosis. The possibility is suggested that it is metabolically different from ordinary diabetes and that it is caused by factors other than failure of production of insulin by the pancreas.

DISCUSSION

JOSEPH H. BARACH, M.D., (*Pittsburgh*): Because of present-day limitations in our knowledge of the eti-

ology of diabetes mellitus, I believe it will be better to project this discussion from the viewpoint of the diabetic patient with retinopathy rather than to attempt to describe special types of diabetes in which retinopathies are commonly found.

In the past, attempts have been made by various workers in this field to classify or group diabetics into types, but I have yet to see any classification or delineation of this disease that can stand up under critical analysis. However, in deference to Dr. Dana's approach to this problem, one must admit that if there is one group to which the term "type of diabetes" might be applied, it would be the Kimmelstiel-Wilson type of case. If and when it can be proved that the vascular lesions in the retina and the lesions in the renal glomeruli are of the same nature, and have a common origin, one would be justified in speaking of cases with these lesions as representing a "type" of diabetes mellitus. As things are, however, ultimate proof for this awaits final acceptance.

I have studied a group of 335 cases of diabetes, searching diligently for common denominators and leads toward a better understanding of the causes and mechanisms of this disease and its complications. These patients, having been seen within the past year, have been under more or less continuous care, some of them for more than thirty years, so that the natural course and evolution of their disease should reflect the pathologic processes inherent in diabetes mellitus.

One-third of the 335 cases showed retinal lesions when they first came for diabetic control. Two-thirds of the cases having retinopathy were between 50 and 70 years of age. Greater obesity was not associated with higher incidence or more serious retinal lesions. Hypertensive diabetics showed a higher incidence and greater severity of retinal lesions than diabetics without hypertension. Nevertheless, some of our hypertensive diabetics escaped retinal lesions for as long as 27 years. (In my experience it is not true that all diabetics will have retinal lesions after 20 to 25 years.) Of diabetics with retinopathy, 88 per cent required insulin, while in the general run of cases, only 60 per cent required insulin. Retinopathy may develop in cases of well-controlled diabetes, but these show fewer lesions and the lesions are less destructive than in poorly controlled cases. An increase in the blood cholesterol was found in 53 per cent of diabetics with retinopathy, and an increase in the S_f 12-20 lipoproteins in 40 per cent.

If the studies that are now being made prove that there is a positive relationship between lesions of the retinae and of the renal glomeruli, as seen in Kimmelstiel-Wilson disease, it will mark progress in our knowledge of diabetes and its complications.

JOSEPH T. BEARDWOOD, JR., M.D., (*Philadelphia*): I wish to say a few words concerning our clinical observation in cases of diabetic retinitis, particularly in association with Kimmelstiel-Wilson's disease. The clinical diagnosis of the latter is often impossible before autopsy findings, as frequently the same clinical picture is seen in patients with chronic urinary infections, particularly in the female. I think we are still at a loss to say what determines the development of this syndrome. The adrenal gland has been suggested as playing some part in this condition and it was of interest to us that in two recent cases in which Addison's disease developed, after six years and twenty years of diabetes respectively, no intimal lesions were noted at the time the Addison's disease was discovered. Why is it that this condition usually does not develop after ten years of diabetes? Why is it that many diabetics do not develop it even after twenty years of diabetes?

My experience has differed from that of Dr. Dana in that I have found patients developing retinitis who have been ofttimes severe diabetics and we have not seen any great improvement in their diabetes following the development of retinitis, which could not be attributed to more meticulous care of their disease because of the threat of oncoming blindness. My associates and I have recently checked 360 cases of diabetes with retinitis and there seems to be a definite difference in the incidence of retinitis in those cases adequately controlled as compared to those in which we feel the diabetes was not controlled according to our standards.

We have also been impressed with the number of juvenile diabetics who do well for five or ten years and then disappear from observation and apparently become careless about their disease for two or three years and report back with typical lesions in the eye and the clinical picture of early Kimmelstiel-Wilson's disease.

It has been our experience also that generalized systemic atherosclerosis is not necessarily part of this picture and that many patients have advanced peripheral and coronary atherosclerosis, but show no evidence of retinal change, and that many patients with well advanced retinitis will have little, if any, evidence of generalized atherosclerosis. There is obviously an unknown factor in these individuals, but from our standpoint we feel that proper control of the diabetes continuously, prompt treatment of urinary infections and in those patients who have increased capillary fragility, the use of antifragility drugs, are of definite value and are prophylactic measures of importance.

ARNOLD LAZAROW, M.D., (*Cleveland*): What per cent of your patients with Kimmelstiel-Wilson's syndrome showed a complete disappearance of the diabetes or showed a diminution in their insulin requirement? What is the order of magnitude of the decreased insulin requirement? I am particularly interested in these findings because of our observations reported last year concerning disappearance of alloxan diabetes in rats. In these animals the diabetes disappeared after it had been present for 12 to 20 months.

HENRY T. RICKETTS, M.D., (*Chicago*): We were all intrigued, I am sure, by Dr. Dana's statement that the patients who develop Kimmelstiel-Wilson syndrome are not those who have experienced acidosis. I should like to ask him in this connection how many of his patients with the Kimmelstiel-Wilson syndrome were originally juvenile diabetics. If there were an appreciable number in this category who were originally juveniles and who never went into acidosis or had a tendency thereto, it would be indeed surprising.

GEORGE W. DANA, M.D., (*Baltimore*): Dr. Barach and Dr. Beardwood have presented other aspects of this general problem, and I think it is important to have all sides of the problem explored.

In answer to Dr. Ricketts' question regarding onset of diabetes in the juvenile phase, our series was an adult series and there were only three or four patients who had onset of diabetes in youth. The problem of juvenile diabetes is different from that in adults.

As for Dr. Lazarow's comments, in 60 per cent of our cases with the Kimmelstiel-Wilson lesions demonstrated at autopsy, there was a real decrease in insulin requirement. One patient who had needed 80 units finally required no insulin at all; this patient almost went into spontaneous hypoglycemia. Approximately 10 patients required no insulin as the Kimmelstiel-Wilson syndrome progressed.

Patients who have been on the same dosage of insulin for a prolonged period should be watched carefully if this syndrome develops, to avoid danger from hypoglycemia.

The Use of Lipotropic Factors in the Treatment of Liver Disease

Studies in animals have demonstrated that a pathologic picture resembling that of portal cirrhosis may be produced experimentally by various methods. In certain instances, the use of lipotropic factors is of prophylactic and therapeutic value. This beneficial effect has been attributed largely to the stimulation of phospholipid formation.

In human beings with liver disease the therapeutic value of choline and methionine has not been definitely established. Since the phospholipid turnover in the liver is probably reflected by the amounts of newly formed phospholipids in the plasma, the use of radioactive phosphorus provides a method for determining the rate of phospholipid turnover and evaluating the effects of lipotropic agents.

In normal persons studied in this manner the rate of phospholipid turnover remains fairly constant for periods up to 6 months. A large dose of choline or methionine (10 gm.) does not increase the phospholipid turnover.

In cirrhotic patients with fatty infiltration of the liver proven by biopsy, a significant increase in the rate of phospholipid turnover is usually demonstrable after a single dose of choline or methionine. Failure of the phospholipid turnover to show such a response initially is believed to be a bad prognostic sign. This response to stimulation is no longer present after 8 weeks of treatment, when the liver fat has decreased or disappeared.

In patients having cirrhosis without fatty infiltration and in patients with uncomplicated infectious hepatitis, the rate of phospholipid turnover is not stimulated by choline or methionine.

Choline or methionine is indicated only at the beginning of treatment in patients with fatty infiltration of the liver who are acutely ill and cannot eat. The same lipotropic effect is achieved more slowly without choline or methionine in patients who will eat an adequate diet.

From an article by David Cayer, M.D., and W. E. Cornatzer, M.D., in *Gastroenterology*, March 1952.

Screening Tests for Diabetes

A Study of Specificity and Sensitivity

Arnold B. Kurlander, M.D., M.P.H., Albert P. Iskrant, M.A.,†*
M. E. Kent, M.D., M.P.H.‡

Washington, D.C.

In January 1952, a multiple screening project was initiated at the Out-patient Department of D. C. General Hospital in Washington, D. C. One of the purposes of this project was to study the results of some of the tests for diabetes in relation to the diagnosis established in the Medical Diagnostic Clinic and thus to investigate the efficiency of these tests as case-finding procedures for diabetes.

The D. C. General Hospital is a municipal hospital providing free medical care to the indigent. It functions as a teaching hospital for Georgetown and George Washington Medical Schools. The staff of the Medical Diagnostic Clinic consists of resident physicians and internes under the direct supervision of the Chief of the Outpatient Department who is an internist certified by the American Board of Internal Medicine.

METHODS OF STUDY

Persons included in this study were referred from the admitting office of the Out-patient Department of the hospital to the Medical Diagnostic Clinic. As many as possible of these persons received a multiple screening examination which included a venous specimen of blood tested by the Wilkerson-Heftmann method to show a blood sugar level above 130 mg. per 100 ml. and if positive again tested to show a blood sugar level above 180 mg. per 100 ml. A urine specimen was tested for sugar by a copper reduction method (Clinitest). In all, 964 persons attending the Out-patient Clinic received a screening examination. Of this number, 953 received the copper reduction test of urine and 928 the Wilkerson-Heftmann test of blood. (The Clinitron, an apparatus for the mechanical performance of the Wilkerson-Heftmann test, was out of order for a brief time.) From these screenees, persons who were going to the Diagnostic Clinic were selected at random to receive a complete diagnostic study requiring three-and-a-half hours, including special examinations for diabetes. This special group of screenees selected for diabetes examination received additional screening tests for diabetes, using the original screening samples of blood and urine: a quantitative blood sugar test by the Somogyi-Nelson method and a test of the urine by a bismuth reduction test (Galatest). This resulted in a Somogyi-Nelson blood test for 605 persons and a bismuth reduction test for 648 persons.

Of the persons referred to the Diagnostic Clinic, only 295 received the complete battery of tests and special diagnostic study for diabetes. This number is less than half of those who were requested to return for a glucose tolerance test and indicates the need for personnel for follow-up work in studies such as these. The diagnostic study for diabetes included a standard three-hour 100 gm. oral glucose tolerance test following three days of full customary meals. The Somogyi-Nelson quantitative method was used for the blood sugar tests on venous blood. When the original blood-sugar level was over 180 mg. per 100 ml., the glucose tolerance test was omitted and a single blood sugar determination after a full meal was substituted.

RESULTS OF TESTS FOR DIABETES

The criteria for positivity of the glucose tolerance tests were based more on the shape than on the height of the blood sugar curve. In general, a curve which returned to 110 mg. per 100 ml. at the end of three hours was considered normal. This held true even though the peak of the curve may have been above 180 mg. per 100

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ml. Conversely, any curve which was above 110 mg. per 100 ml. at the end of three hours was usually considered diagnostic of diabetes. Exceptions to these criteria were made in cases where other diseases were believed to account for abnormality or where special features of the curve seemed to demand a different interpretation. For cases screening over 180, the Somogyi-Nelson test was repeated two hours after eating and a venous blood sugar reading over 150 was considered diagnostic.

TABLE 1
Summary of the tests

Type of Investigation	Number of Persons
Multiple screening tests	964
Urine test by copper reduction method (Clinitest)	953
Urine test by bismuth reduction method (Galatest)	648
Blood test by Wilkerson-Heftmann method	928
Blood test by Somogyi-Nelson method	605
Complete diagnostic study for diabetes	295

The population screened is described as to race, sex and age in Table 2. It will be noted that the population, in addition to being indigent, is predominantly non-white; more than half the persons tested were non-white females. The median ages were in the fifties for white males, in the forties for white females and non-white males, and in the thirties for non-white females. Obviously, then, the screened population is much older than the general population of the United States but, because of their age, a good group to screen for diabetes.

TABLE 2
Race, sex and age distribution of 964 persons receiving multiple screening tests

Age Group	White		Non-white	
	Male	Female	Male	Female
Total	66	70	274	554
15-19	1	3	17	38
20-29	2	7	35	118
30-39	3	13	49	150
40-49	18	15	66	125
50-59	26	19	50	62
60-69	8	11	40	45
70-79	4	2	16	14
80-89	4		1	2

COMPARISON OF TEST METHODS

In the following tables only cases were used that received the tests being compared. Obviously then, fewer cases are included in tables where the four tests are being compared than where two tests are being compared. Where only one test is

TABLE 3
Results of diabetes screening by method and hours after eating for the 478 persons tested by all four methods

Method	Hours since eating	Number tested	Positive	
			Number	Per cent**
Blood sugar test Wilkerson-Heftmann method positive—over 130 mg. per ml.	Total	478	41	8.6
	Fasting*	236	17	7.2
	2 or more	131	12	9.2
	Less than 2	104	10	9.6
	Not stated	7	2	—
Blood sugar test Somogyi-Nelson method positive—over 130 mg. per ml.	Total	478	41	8.6
	Fasting*	236	17	7.2
	2 or more	131	12	9.2
	Less than 2	104	10	9.6
	Not stated	7	2	—
Test for sugar in urine Copper reduction method (Clinitest) positive—trace or more	Total	478	89	18.6
	Fasting*	236	33	14.0
	2 or more	131	32	24.4
	Less than 2	104	23	22.1
	Not stated	7	1	—
Test for sugar in urine Bismuth reduction method (Galatest) positive—trace or more	Total	478	55	11.5
	Fasting*	236	16	6.8
	2 or more	131	22	16.8
	Less than 2	104	16	15.4
	Not stated	7	1	14.3

* The individuals had not eaten since the night before. All tests were made between 8:30 a.m. and 10:30 a.m.
**Percentages have been calculated in this and subsequent tables, even when numbers are small, for ease in rough comparisons. The calculation to one decimal place in no way signifies that small differences are meaningful.

being analysed the numbers are correspondingly larger. For example, where only the Somogyi-Nelson method is involved, as in Table 9, 23 previously undiagnosed diabetics are included; in Table 6 only 21 are included, as two of the cases did not receive all four tests. Unequal numbers were used to make maximum use of the small number of cases of diabetes.

Table 3 shows the number tested for diabetes by each of the four methods for those persons receiving all four of the tests, the number of hours since last eating and the number screening positive. (Readings of 130 mg. per 100 ml. for the Wilkerson-Heftmann and trace or more for the urine determination were considered positive.) It is noted that the percentage screening positive is quite high. "Glycosuria" was found in 18.6 per cent by the copper reduction test of the urine and in 11.5 per cent by the bismuth reduction test. "Hyperglycemia" was found in 8.6 per cent by the Wilkerson-Heftmann and the Somogyi-Nelson methods. As may be expected, the percentage screening positive is lower for persons fasting. (Fasting is defined as not having eaten since the night before. All screening was performed between 8:30 a.m. and 10:30 a.m.)

In Table 4, the results of the tests by the Wilkerson-Heftmann method showing the blood sugar both over 130 mg. per 100 ml. and 180 mg. per 100 ml. are compared with the results of testing by copper reduction and bismuth reduction methods. While the figures are small, it appears that a person who screens positive to the Wilkerson-Heftmann test at 180 mg. per 100 ml. is likely to screen positive to urine tests. Of those screening positive at 130 mg. per 100 ml. but not at 180 mg. per 100 ml. to the Wilkerson-Heftmann test, the proportion screening positive to the urine tests is rather low, being lowest when the subjects were fasting. Conversely, many persons with tests negative to the Wilkerson-Heftmann procedure at 130 mg. per 100 ml., had positive urine tests. Within the limits of these data, then, and without

TABLE 4

Results of blood sugar tests by the Wilkerson-Heftmann method compared with tests for sugar in the urine by the copper reduction and bismuth reduction methods for the 636 persons tested by the three methods

Blood sugar—Wilkerson-Heftmann method			Sugar in urine—Copper reduction method (Clinitest)				Sugar in urine—Bismuth reduction method (Galatest)			
			Positive		Negative		Positive		Negative	
Results (findings)	Hours since eating	No. tested	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Blood sugar over 180 mg. per 100 ml.	Fasting	7	7	100.0	0	0.0	6	85.7	1	14.3
	2 or more	5	5	100.0	0	0.0	5	100.0	0	0.0
	Less than 2	6	6	100.0	0	0.0	6	100.0	0	0.0
	Total	18	18	100.0	0	0.0	17	94.4	1	5.6
Blood sugar over 130 mg. but not over 180 mg.	Fasting	10	2	20.0	8	80.0	2	20.0	8	80.0
	2 or more	7	4	57.1	3	42.9	3	42.9	4	57.1
	Less than 2	4	1	25.0	3	75.0	1	25.0	3	75.0
	Not stated	2	0	0.0	2	100.0	0	0.0	2	100.0
	Total	23	7	30.4	16	69.6	6	26.1	17	73.9
Blood sugar under 130 mg.	Fasting	285	31	10.9	254	89.1	14	4.9	271	95.1
	2 or more	169	30	17.8	139	82.2	17	10.1	152	89.9
	Less than 2	124	20	16.1	104	83.9	12	9.7	112	90.3
	Not stated	17	2	11.8	15	88.2	4	23.5	13	76.5
	Total	595	83	13.9	512	86.1	47	7.9	548	92.1

TABLE 5

Comparison of results of blood sugar tests by Somogyi-Nelson and Wilkerson-Heftmann methods for the 572 persons tested by both methods

Blood sugar tests by Somogyi-Nelson method mg. per 100 ml.		Blood sugar tests by Wilkerson-Heftmann method mg. per 100 ml.			Total	
		Less than 130	130-179	180 or more	No.	Per cent
Less than 130		509	7	0	516	90.2
130-179		8	22	1	31	5.4
180 or more		0	3	22	25	4.4
Total	Number	517	32	23	572	
	Per cent	90.4	5.6	4.0		100.0

consideration of the diagnosis of diabetes, it would seem that the urine test is not a good indication of the blood sugar result in cases with a positive blood sugar test over 130 and less than 180 mg. per 100 ml. of blood.

In Table 5 are shown the results of the blood sugar tests by the Somogyi-Nelson method and the Wilkerson-Heftmann method for the 572 persons tested by both methods. The agreement between the results of these two methods was almost perfect as far as percentages are concerned, although there was a difference in individual instances. The results of the two methods were in disagreement in 19 of the 572 cases in which tests were made by both methods. In 12 of the 19 instances of disagreement the difference was more than 10 mg. per 100 ml.

SPECIFICITY AND SENSITIVITY OF TESTS

Sensitivity may be defined as the ability of the test to classify as positive those who have the condition being screened for and is calculated as the percentage screening positive of those diagnosed as having diabetes. For example, the Somogyi-Nelson method at 130 mg. per 100 ml. screened positive 15 persons of the total of 23 persons diagnosed as having diabetes and so the sensitivity rating is 15/23 or 65.2 per cent (see Table 9). *Specificity* may be defined as the ability of the test to classify as negative those who do not have the condition being screened for and is calculated as the percentage screening negative of those determined not to have diabetes. For example, the Somogyi-Nelson method at 130 mg. per 100 ml. screened negative 245 persons of the total of 250 persons confirmed as not having diabetes and so the specificity rating is 245/250 or 98.0 per cent (see Table 9). Another measurement commonly used to evaluate screening is the proportion of the positives who are diagnosed as having the condition. Obviously this latter measurement of the test is a function of the prevalence of the condition (unlike specificity and sensitivity indices, which are independent of the prevalence) but is a good measurement of the efficiency of the test for areas of similar prevalence.

The group included in this portion of the paper is limited to those persons for whom diagnostic observations were made for diabetes by a physician who did not know the results of any screening test.

It is important to point out here that the cases of diabetes (23) used in determining sensitivity ratings were those discovered as a result of a complete diagnostic survey including special examinations for diabetes. They do not include previously known diabetics, nor are they limited to diabetics with symptoms or those discovered through a screening examination. It might be expected that few, if any, unknown cases of diabetes would be present among those screening negative to the usual tests. This was not so among persons screened in the Out-patient Department at D. C. General Hospital. Whether these results were influenced by the age of the population tested, or existing conditions other than diabetes, or the nutritional status of those screened, is not known. The results were obviously influenced by the large proportion of persons screened who had not eaten recently. Studies such as this must be expanded to other population groups before these points can be settled.

Table 6 shows the results obtained through urine tests by the copper reduction (Clinitest) and bismuth reduction (Galatest) methods. It is noted that less than half of the previously undiagnosed (new) cases of diabetes showed positive reactions to these screening tests and that many nondiabetics also showed false positive reactions.

When only specimens showing a reaction graded 1-plus or more are considered positive, then the specificity of both tests is increased greatly. Of those persons diagnosed as not having diabetes only 2.9 per cent showed a false positive reaction to the copper reduction method and 1.7 to the bismuth reduction method considering reactions graded 1-plus or more. No nondiabetic screened positive to either test with a reaction graded 3-plus or more. It would appear then that, under conditions as they existed in this hospital, urine tests reported as showing a trace of sugar could be ignored as far as the follow-up of diabetes is concerned and that tests graded 3-plus or more are very likely to mean diabetes. Conversely, it would appear that many cases of early diabetes will be missed if dependence is placed on screening by tests of the urine, even if it is decided to follow up the slightest positive reaction.

Table 7 shows the results by the Somogyi-Nelson and the Wilkerson-Heftmann methods. A vast increase in efficiency over the urine tests is seen. At 130 mg. per 100 ml. the specificity ratings were 98.0 and 96.8. This means that 98 per cent of nondiabetics will screen below 130 mgs. per 100 ml. by the Somogyi-Nelson method and 96.8 per cent will screen negative by the Wilkerson-Heftmann method at the 130 level. These percentages seem satisfactory but the sensitivity levels may be considered low—65.2 and 56.5; that is 34.8 per cent of the newly diagnosed diabetics had Somogyi-Nelson readings below 130 and 43.5 per cent had negative screening results by the Wilkerson-Heftmann method at the 130 level.

The results of all four methods are summarized in

TABLE 6

Results of tests for sugar in the urine by copper reduction and bismuth reduction methods according to the presence or absence of diabetes in 269 cases in which both tests were used*

Diagnosis and result of tests	Copper reduction method (Clinitest)		Bismuth reduction method (Galatest)	
	Number	Per cent	Number	Per cent
Not diabetes	239	100.0	239	100.0
Negative	205	85.8	223	93.3
Trace or more	34	14.2	16	6.7
1+ or more	7	2.9	4**	1.7**
2+ or more	1	0.4	1**	0.4**
3+ or more	0	0.0	0**	0.0**
4+ or more	0	0.0	0**	0.0**
Newly discovered diabetes	21	100.0	21	100.0
Negative	14	66.7	13	61.9
Trace or more	7	33.3	8	38.1
1+ or more	7	33.3	6	28.6
2+ or more	6	28.6	5	23.8
3+ or more	5	23.8	5	23.8
4+ or more	4	19.0	5	23.8
Previously known diabetes	9	100.0	9	100.0
Negative	3	33.3	3	33.3
Positive	6	66.7	6	66.7

* Includes only cases with known diagnosis and known results.
**For 2 nondiabetics the report of the bismuth reduction test was "positive." They are included as a "trace or more" but not in the "1+ or more."

TABLE 7

Results of blood sugar tests by Somogyi-Nelson and Wilkerson-Heftmann methods according to the presence or absence of diabetes for the 281 persons receiving both tests*

Diagnosis and result of test	Somogyi-Nelson method		Wilkerson-Heftmann method	
	Number	Per cent	Number	Per cent
Not diabetes	250	100.0	250	100.0
Negative	245	98.0	242	96.8
Positive (over 130 mg. per 100 ml.)	5	2.0	8	3.2
Newly discovered diabetes	23	100.0	23	100.0
Negative	8	34.8	10	43.5
Positive (over 130)	15	65.2	13	56.5
Previously known diabetes	8	100.0	8	100.0
Negative	1	12.5	1	12.5
Positive (over 130)	7	87.5	7	87.5

* Includes only cases with known diagnosis and known results.

Table 8. It is noted that even when all four tests were done on each screenee, over one-quarter of the previously undiagnosed diabetics screened negative to all tests (or 71.4 screened positive to at least one of the four tests) with the conditions under which screening was carried out at D. C. General Hospital at random times after eating. Fourteen of the 21 newly diagnosed diabetes cases were screened fasting and only 4 were tested within two hours of eating.

In cases ultimately proved to have newly discovered diabetes the blood sugar screening level (by the Somogyi-Nelson method) was as low as 84; in 8 of the 23 cases, the blood sugar was below 130 mg. per 100 ml. Table 9 shows the sensitivity and specificity ratings testing with the Somogyi-Nelson method at various levels. It will be noted that no case of undiagnosed diabetes screened below 80 mg. per 100 ml. and no person without diabetes screened above 190 mg. per 100 ml. This is a wide range, since only 23 cases of undiagnosed diabetes are included.

TABLE 8

Sensitivity and specificity levels of diabetes screening methods for the 21 newly diagnosed cases of diabetes and the 226 nondiabetics all of whom received the four tests (at random times after eating)

Method	Sensitivity		Specificity	
	Number Positive	Per cent	Number Negative	Per cent
Test for sugar in urine				
by copper reduction method	7*	33.3	192	85.0
by bismuth reduction method	8*	38.1	210	92.9
Blood sugar test				
Wilkerson-Heftmann method over 130 mg. per 100 ml.	12	57.1	219	96.9
Somogyi-Nelson method over 130 mg. per 100 ml.	14	66.7	221	97.8
Positive result on one of four tests	15	71.4		
Negative results on all four tests			183	81.0

* Trace or more

TABLE 9

Sensitivity and specificity ratings of the Somogyi-Nelson test method at various levels at random* times after eating for the 273 persons receiving this test and also a complete diagnostic study

Blood sugar level	Sensitivity	Specificity
If this level were considered positive (mg. per 100 ml.)	This per cent of newly diagnosed diabetics (23) would screen positive	This per cent of nondiabetics (250) would screen negative
80	100.0	40.8
90	95.7	66.8
100	87.0	82.4
110	73.9	91.2
120	69.6	97.2
130	65.2	98.0
140	56.5	98.8
150	52.2	99.2
160	39.1	99.6
170	30.4	99.6
180	26.1	99.6
190	21.7	100.0

* Without regard to lapse of time since eating.

It must again be emphasized that these results are among persons screened at random times after eating in an out-patient clinic population. When the population is classified according to time after eating, one finds that there were only four diabetics who received postprandial blood tests and three of them had positive tests. Obviously then, these results cannot be applied to nonclinic population groups where screening may be much closer to the time of eating and where the renal threshold for glucose may be different. The results of this study, however, do indicate the need for similar studies among other groups and under more controlled conditions to determine screening levels which will give optimum balance between sensitivity and specificity. The Division of Chronic Disease and Tuberculosis has already initiated such a study at Boston City Hospital (Boston, Mass.), under the direction of Dr. Hugh L. C. Wilkerson.

SUMMARY

In a multiple screening project in the Out-patient Department of the D. C. General Hospital, the efficiency of four tests as diabetes case-finding procedures was investigated. Venous blood samples were tested for sugar by the Wilkerson-Heftmann and Somogyi-Nelson methods, and urine samples were tested by a copper reduction method (Clinitest) and by a bismuth reduction method (Galatest). Diagnoses were established by independent investigation in the Medical Diagnostic Clinic. The sensitivity and specificity of these four tests were compared. Sensitivity—the test's ability to classify as positive those who have the condition being screened for—was calculated as the percentage screening positive of those diagnosed as having diabetes. Specificity—the test's ability to classify as negative those who do not have the condition being screened for—was calculated as the percentage screening negative of those determined not to have diabetes.

Among this outpatient clinic population (screened at random times after eating) blood tests gave superior results to urine tests. The specificity ratings of blood sugar tests by the Somogyi-Nelson and Wilkerson-Heftmann methods were satisfactory—98.0 and 96.8 per cent respectively; these figures would indicate that almost all

the nondiabetics were properly classified by the screening test. However, the sensitivity ratings were low—65.2 and 56.5 per cent respectively, which would indicate that a relatively low percentage of the diabetics was detected by the screening test at the 130 mg. per 100 ml. level. In other words, 34.8 and 43.5 per cent respectively of those diagnosed as having diabetes had screening levels below 130 mg. per 100 ml. and theoretically would have been missed if that level had been arbitrarily set as the detection level.

The results of this study indicate a need for similar investigations among other population groups and under conditions subject to better control to determine the most efficient screening levels.

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The Common Cause

This is the century of the biological sciences. The physical sciences have already achieved a high degree of consistency and conceptual maturity. In the life sciences, on the other hand, analytical understanding is still no more than rudimentary, unifying concepts are still scarce, and many fundamental principles remain to be discovered. The major job still lies ahead. At the same time, the urgency of the task grows, as mankind looks expectantly to new advances in agriculture, public health, and medicine, whose rational development depends on biological knowledge and understanding.

Biology has grown in volume and diversity to the point where it would be far beyond the capacity of any one individual to acquire competence in more than a limited sector of the field. Biologists, in the sense of miniature incarnations of universal biological knowledge, no longer exist. Biological science has become a group enterprise with many servants in varied stations. The single-celled organism has evolved into a multi-cellular one, and its health, survival and growth depend on the harmonious cooperation of its many specialized members. Anyone contributing to this collective task, constructively, competently, and conscientiously, thus becomes a biologist. Consequently, it takes all kinds of biologists to make the biological world, none of them able to carry on without the others. And biology needs their full diversity.

It needs the observer, the gatherer of facts, the experimenter, the statistician, the theorist, the classifier, the technical expert, the interpreter, the critic, the teacher, the writer. It needs the student of evolutionary history as much as it does the experimental physiologist; the precise recorder of morphological data as much as the analytical biophysicist and biochemist; the investigator of molecular interactions as much as the student of supramolecular organization, of the order of events in space and time. It needs the help of all hands at all stations, from the research man who conceives a new idea, to the assistants who prepare solutions or tend cultures or animals; from the mechanic who builds a new instrument, to the artist or photographer who prepares indelible records of microscopic specimens or physiological tracings; and last, not least, from the man who willingly gives of his time and effort in order to help obtain and distribute some of the most basic tools of science—fellowships, research grants, materials and jobs—to the one who willingly accepts them to good advantage. They all work for a common cause and should feel above the unjustified and undignified popularity contests that center on such monomaniac questions as who is "more important," the "fundamental" or the "applied" scientist; the explorer or the instructor; the technical expert or the philosopher. They are all needed—in their proper stations. And they should be rated not by *what* they are doing but by *how* they are doing it.

From "The Challenge of Biology" by Paul Weiss, Ph.D., M.D., in *Science*, July 1953.

Effect of Antihyaluronidase on the Capillary Fragility of the Diabetic

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The spreading factors were first observed by Duran-Reynals in the course of the study of the effect of testicular extract on vaccinial infection.[1] Soon afterward, it was found that the rapid penetration of tissues by certain pathogenic bacteria and by the venom of poisonous snakes and insects was also due to spreading factors.[2] Studies of mesodermal polysaccharides demonstrated that the spreading effect was produced by the action of the enzyme hyaluronidase. This enzyme has the property of converting a viscid medium into a fluid one.

It has been recognized that hyaluronidase has an effect on capillary permeability, but the site of its action in producing this effect is controversial. There is some evidence to indicate that the effect on the capillaries is direct.[3] However, it is difficult to consider capillary permeability without considering the permeability of the supporting tissues. For this reason Zweifach and Chambers[4] investigated the effect of hyaluronidase on the connective tissue ground substance. Their work indicated that the enzyme acts on the gelatinous matrix of the supporting structures of the capillary vessels rather than on the interendothelial cement. Changes in the interstitial supporting tissues permit abrupt rupture of traumatized capillaries and extravasation of blood along the vessel wall.

The hypothesis considered here is that the effect of hyaluronidase inhibitors (hereinafter referred to as antihyaluronidase) might be to influence the interstitial supporting structures so that spreading from injured capillaries would be decreased; it is assumed that the effect would be a splinting of the capillaries. Diabetics were chosen for study because of the high incidence of increased capillary fragility in this group. The recent concepts of a disturbance in mucopolysaccharide metabolism in diabetes[5,6,7] also suggested that study of these patients might be rewarding. If it could be demonstrated that antihyaluronidase protects the fragile capillaries of the diabetic from rupture by trauma it might be of value in protecting the retinal vessels of the diabetic.

METHOD OF STUDY

Thirty-two white female diabetic patients from the Medical and Surgical Wards of Bellevue Hospital were selected for study. The only requisites were that the patients not be bedridden and be capable of being transported to the photographer.

Antihyaluronidase* dissolved in normal saline, 1 cc. containing 50 mg., was injected subcutaneously into the antecubital fossa of one forearm, and 1 cc. of normal saline was similarly injected into the corresponding site of the opposite forearm. The treated sides, the controls and the sequences of the injection of both antihyaluronidase and normal saline were purposely given without special systematic selection. The point of injection was always one inch below the crease of the elbow. Twenty minutes after the injections, blood pressure readings were taken on both arms. When the readings were stabilized, the pressure was maintained midway between systolic and diastolic levels for ten minutes. Five minutes later an area one inch square with the point of injection at the center was photographed. The petechiae appearing in this square were counted twice by two different observers.

RESULTS

The injection of antihyaluronidase into the forearm occasionally resulted in a slightly painful reaction. The point of injection often bled for a few minutes, prob-

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*The antihyaluronidase (SC-3859) for this study was supplied by Dr. Irwin C. Winter of G. D. Searle and Company.

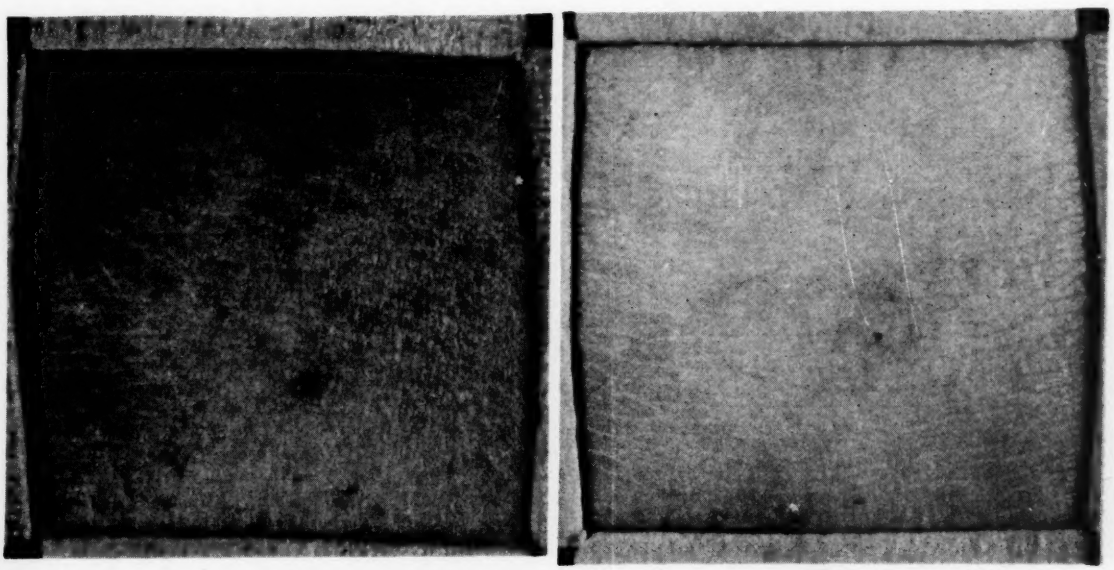
ably because of the heparin-like action of the preparation used. No pressure was applied to the bleeding point. In contrast to the saline which spread through the subcutaneous tissues rapidly and was imperceptible at the site of injection within a few minutes, antihyaluronidase remained as an elevated, nonindurated, erythematous area for two or three days after the injection. Nevertheless, tourniquet tests, which were done twenty minutes after the injection, showed a difference in the quality as well as in the number of petechiae on the two sides. In many instances, the petechiae on the antihyaluronidase side were not so distinct nor so discreet as those on the saline side. They appeared faded and under magnification their outlines were ill-defined. (Figure 1a and 1b.)

Since the photographed area was one inch square, the number of petechiae accepted as normal was approximately that which was defined as normal in the 2.5 cm. circle described in the Wright-Lilienfeld modification of the Rumpel-Leede test; that is, 10 to 15 with an upper limit of 20. Greater accuracy of definition than this was considered unnecessary for this work.

Six of the 32 patients studied had normal capillary fragility according to these standards. Of these, five showed no appreciable difference in the number of petechiae when the saline and antihyaluronidase forearms were compared. One patient had no petechiae in either window. In four who had increased capillary fragility, there was no perceptible difference in the number of petechiae on the two forearms. The notations on these patients did not reveal any accountable common denominator. In the remaining twenty-two patients the effect of antihyaluronidase was most striking in those who had the greatest capillary fragility. In all our patients the effect was not localized to the area injected but extended over the entire forearm and hand. (Figure 2a and 2b.)

The petechiae in the photographs were counted and the number on the control side was compared with that on the treated side. Counting the petechiae was difficult because many were indistinct, especially on the side treated with antihyaluronidase. In addition, when several hundred petechiae appeared in the area that was being counted, it was impossible to be sure that the results were accurate. If the results of the four counts made of one area varied widely, further counts were made. These were averaged and the figures for the 32 cases were analyzed.

In the 22 cases in which the petechial counts showed a difference between the forearms injected with saline and with antihyaluronidase, the count was smaller on the side treated with antihyaluronidase (Figure 3). This difference would be expected by chance less than 1 in 20 times and is therefore significant.



A B

FIGURE 1. (a) Forearm treated with saline. (b) Forearm treated with antihyaluronidase. Patient M.C., aged 70 years, maintained on diet containing 180 gm. of carbohydrate with regular insulin as required. The point of injection is visible in both photographs. There are clearly fewer petechiae on the side treated with antihyaluronidase.

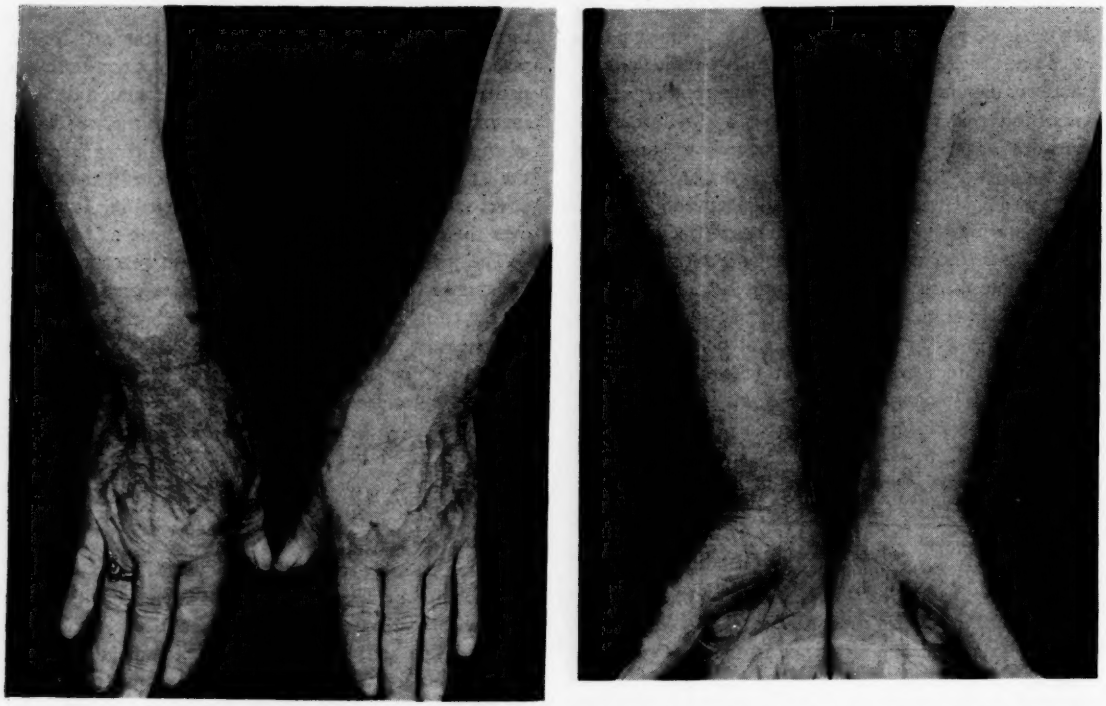


FIGURE 2. Patient B.R., aged 76 years, treated with diet containing 180 gm. of carbohydrate without insulin. Antihyaluronidase was given subcutaneously into the left antecubital fossa. The dorsal and flexor aspects of the hands, wrists and forearms indicate that the effect of antihyaluronidase was widespread. A localized reaction to antihyaluronidase can be seen on the left.

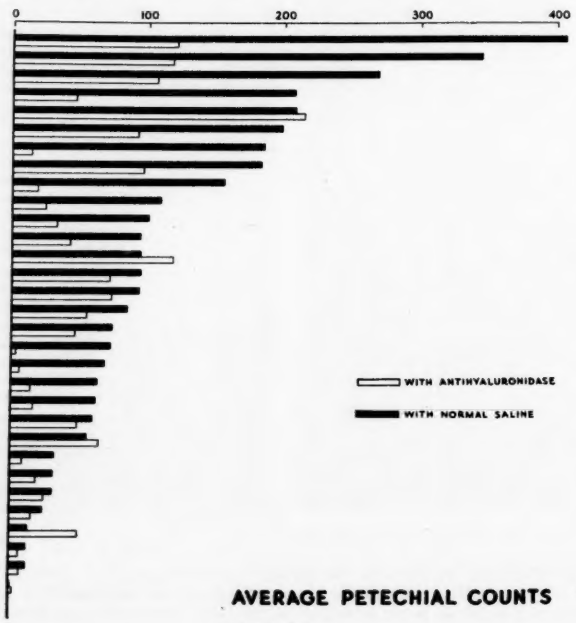


FIGURE 3.

There was an average of 57.7 petechiae on the forearms injected with saline. Since the patient variation was great, this sample is not very reliable. On the forearms treated with antihyaluronidase, the mean number of petechiae was 25.6. As a description of the typical number of the counts, the arithmetic mean (average) is not very satisfactory since this measure is pulled upward appreciably by a few high counts. However, another measure, the median, has the advantage of greater stability for describing the typical petechial count. The median for the saline treated forearm was 34 in the area counted; that is, 50 per cent of the patients had counts below 34. In the forearms treated with antihyaluronidase, the median was only 15.5.

Although the patient variations on which the means (averages) are based are wide, a test of the significance of the difference between the sides treated with saline and with antihyaluronidase (57.7 minus 25.6) showed that the result, 32.1, is not likely to occur by chance.

Further studies are in progress to determine the means by which antihyaluronidase produces the observed effects.

SUMMARY

1. Capillary fragility tests were performed on 32 female diabetic patients by the positive pressure method after the injection of 1 cc. of a saline solution of antihyaluronidase (50 mg.) subcutaneously into one forearm and a similar amount of normal saline into the other. The point of injection and the method of administration were similar in all instances. The number of petechiae produced was smaller generally on the side treated with antihyaluronidase than on the side treated with saline.

2. In the group with increased capillary fragility, four of the patients were unaffected by treatment with antihyaluronidase. In the remaining 22 patients of this group, the average number of petechiae on the saline injected forearms was 57.7; on the forearms similarly treated with antihyaluronidase, the average number of petechiae was 25.6.

3. The difference in the number of petechiae on the two forearms (57.7 minus 25.6) is statistically significant; that is, the difference is greater than may be expected by chance alone.

ACKNOWLEDGMENT

Grateful acknowledgment is made to Dr. Donald Mainland for his valuable assistance in outlining our work and to Drs. Raymond S. Jackson and Irwin C. Winter for their encouragement and interest.

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Doctors Afield

Every morning before Maimonides started his day's work he repeated his "Prayer of a Physician." This prayer, parts of which are as follows, could well serve as an ideal guide to the physician of today:

. . . Grant that I may be filled with love
For my art and for my fellow-men.
May the thirst for gain and the desire for fame
Be far from my heart.
For these are the enemies of Pity
And the ministers of Hate.
Grant that I may be able to devote myself, body and soul, To Thy children who suffer from pain.
Preserve my strength that I may be able to restore
The strength of the rich and the poor,
The good and the bad, the friend and the foe.
Let me see in the sufferer the man alone.
When wiser men teach me, let me be humble to learn.
For the mind of man is so puny
And the art of healing is so vast.
. . . Let me be intent upon one thing, O Father of Mercy—To be always merciful to Thy suffering children.

From "Moses Maimonides," by Solomon E. Barr, in *The New England Journal of Medicine*, May 6, 1954.

Recent Statistics on Diabetes*

Reflecting extremely favorable health conditions generally, the death rate from diabetes in the early months of 1954 declined sharply below that in the corresponding period of 1953, which was marked by a respiratory outbreak of considerable proportions. Provisional data for the United States, based on a 10 per cent sample of death certificates, showed a death rate from diabetes of 16.9 per 100,000 population in the first quarter of 1954, as compared with 18.9 in 1953. Similarly, in the urban wage-earning population, represented by Industrial policyholders of the Metropolitan Life Insurance Company, the death rate from diabetes declined from 17.0 per 100,000 in the first four months of 1953 to 15.9 in the same period of the current year.

For the entire year 1953, the provisional mortality data on diabetes in the 10 per cent sample showed a very slight decrease in the death rate from 1952. The number of deaths ascribed to diabetes last year is estimated to be about 25,000 or not greatly different from that in each of the four years preceding. In contrast with the experience in the general population, the death rate among the Industrial policyholders of the Metropolitan Life Insurance Company increased more than 8 per cent in 1953 as compared with 1952.

The changes in the death rates from diabetes for the various local areas between the two years were not uniform. As Table 1 shows, the death rate in New York City remained stationary, that in Philadelphia increased nearly 10 per cent between 1952 and 1953, while in both Boston and Baltimore the rates declined very appreciably.

Toronto and Montreal, the two Canadian cities for which data are regularly obtained, both showed an increase in the death rate in 1953 over 1952, the rise being particularly large for Toronto. This trend in the urban Canadian population is confirmed by the data for Industrial policyholders of the Metropolitan Life Insurance Company in Canada, among whom the death rate from diabetes in 1953 was 9.6 as compared with 7.5 in 1952.

For England and Wales figures for the first nine months of 1953 showed a minimal increase in the diabetes death rate over the same period of 1952. This increase was limited to the male population, the rates for females being identical in the two years. Data for London Administrative County for the entire year of 1953 showed a sizable reduction in the diabetes death rate over 1952, but this may reflect conditions peculiar to that area.

Regional data for 1953, based on the 10 per cent sample of death certificates, showed a rather mixed trend in diabetes mortality as compared with the preceding year (see Table 2). In four of the nine geographic areas the death rate in 1953 was higher than that of the year before, but in only one, the East North Central Area, was the increase appreciable. In three of the five areas experiencing a decline, the reduction was appreciable. In the Mountain Area, however, the rates are subject to sharp fluctuations because of the small number of deaths in the sample for this sparsely populated region.

A few years ago the Medical Department of the Fidelity Mutual Life Insurance Company revised its procedure in analyzing the causes of death among its policyholders to bring out the etiological factors in its mortality experience. In this revision deaths were ascribed to diabetes only if diabetic acidosis was the cause of death. However, careful record was made of all cases in which policyholders were known to have diabetes at the time of death. Between 1947 and 1952 inclusive, there were 193 deaths of known diabetics. This was 3.1 per cent of all deaths recorded in the company's experience during the period. As Table 3 shows, only 8, or 4.1 per cent of the deaths of diabetics were due to acidosis and ascribed, therefore, to diabetes. The overwhelming majority—more than four-fifths—of the deaths of diabetics were due to arteriosclerosis. In interpreting these data it should be kept in mind that the clientele of the company consists predominantly of upper-middle-class males. The median age of the entire policyholder group is about 42 years,

*Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual material suitable for this section in future issues, from Association members and other readers of the Journal.

TABLE 1

Recent data on diabetes mortality—deaths and death rates for 1952 and 1953

Area	Death rates per 100,000		Number of deaths	
	1953	1952	1953	1952
United States (10% sample)	16.0	16.2	2,539	2,525
Metropolitan Life Ins. Co.				
Industrial Policyholders	15.6	14.4	2,893	2,674
New York State	21.1	20.6	3,272	3,146
New York City	20.5	20.5	1,660	1,652
Maryland	16.2	19.3	405	473
Baltimore, resident	19.0	22.8	183	218
Boston	21.2	26.7	172	216
Philadelphia	29.4	26.7	626	564
Toronto	18.0	14.2	120	95
Montreal, resident	19.7	17.9	207	185
London (Administrative County)	7.5	9.1	254	307
	Jan.-Sept.		Jan.-Sept.	
England and Wales				
Total	7.5	7.4	2,486	2,443
Males	5.3	5.0	848	795
Females	9.6	9.6	1,638	1,648

Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in *Current Mortality Analysis*, a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2

Number of deaths and death rates from diabetes in geographic division; United States reporting area for the 10 per cent sample: 1951, 1952 and 1953

Geographic Division	Death rates per 100,000*			Number of deaths*		
	1953	1952	1951	1953	1952	1951
U. S. reporting area	16.0	16.2	16.5	2,539	2,525	2,528
New England	18.4	20.2	24.1	178	191	218
Middle Atlantic	22.6	22.2	19.2	702	682	591
East North Central	20.2	19.0	20.1	651	602	623
West North Central	17.3	18.1	17.9	247	256	256
South Atlantic	12.5	12.3	12.9	281	273	279
East South Central	8.9	10.5	12.0	102	120	141
West South Central	10.6	10.5	12.2	162	158	180
Mountain	9.8	14.9	10.8	55	81	56
Pacific	9.9	10.4	12.5	161	162	184

*Excludes armed forces overseas.

These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the *Current Mortality Analysis*.

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 3

Causes of death of policyholders known to have diabetes at time of death

Fidelity Mutual Life Insurance Company, 1947-1952

Cause of death	Number	Per cent
All causes	193	100.0
Diabetic acidosis	8	4.1
Arteriosclerosis (coronary, cerebral, renal, etc.)	159	82.5
Cancer	7	3.6
Pneumonia	5	2.6
Cirrhosis of liver	5	2.6
Prostatic disease	2	1.0
Other*	7	3.6

*One death each from: pulmonary tuberculosis, brain tumor, aplastic anemia, gastric ulcer, pyelonephritis, ruptured urethra and accident.

Source: Dr. Joyce T. Sheridan, Associate Medical Director, The Fidelity Mutual Life Insurance Company, Philadelphia, Pa.

and the median age of death from all causes is about 64 years.

A few years ago, the School Health Act of the Commonwealth of Pennsylvania required that each pupil be given a complete physical examination every two years. This, together with the good records kept by the Division of Medical Services of the Philadelphia Public School system, has facilitated the assembling of statistics on diabetes in Philadelphia Public School children. The data in Table 4 were provided by Dr. Ruth Weaver, Director of Health Services of the Division. This table indicates that since the inauguration of the program an appreciable number of new cases of diabetes have been identified annually. The number of such cases in

TABLE 4

Diabetes in Philadelphia Public Schools, 1948-1953

School Year	Enrollment	Urinalyses	Pupils with diabetes	Previously known	New Cases	Known diabetes deaths
1948-1949	210,645	6,967	60	60	0	0
1949-1950	213,001	5,049	73	60	13	2
1950-1951	212,816	4,951	100	73	27	0
1951-1952	214,103	3,845	120	100	20	1
1952-1953	218,250	230	139*	120	19	1

*Three of these 139 were discovered by "screening" (urinalysis and subsequent study).
Source: Dr. Ruth H. Weaver, Director of Health Services, Philadelphia Public Schools.

the school years 1949-1950 to 1952-1953 among Philadelphia's Public School children has averaged nearly 20 a year, or about 1 in 10,000 pupils. The increase in the total number of known cases may be subject to error, because no allowance appears to have been made in the data for pupils who graduated, were transferred or died, but the figures are at least indicative of the prevalence of diabetes in the public-school age group. The total known number reported in the school year 1952-1953 is equivalent to approximately 1 in 1600 pupils, or somewhat higher than the ratio (1:2500) in this age group in the National Health Survey of 1935-1936.

DIABETES AS A CAUSE OF BLINDNESS

Blindness associated with or due to diabetes accounts for an increasing proportion of total prevalence and incidence of blindness. Major contributing factors are (1) the reduction of blindness due to congenital causes and to infections at birth or in infancy and childhood, (2) the increasing average age of the population, and (3) the increased proportion of diabetics with long duration of the disease among whom the frequency of the development of blindness is rather high. New data for England both on the relative importance of blindness in diabetics, as well as characteristics of the diabetic blind have recently been published in the monograph, "The Causes of Blindness in England, 1948-1950," by Arnold Sorsby (Ministry of Heath, London, 1953). The data are based on certificates obtained through the Southern Regional Association for the Blind and the North Regional Association for the Blind which together serve nearly 90 per cent of the registered blind in England. The data presented here relate to cases with blindness due to the same causes in both eyes.* A great majority of the entire group of blind persons studied did not suffer complete loss of sight—only 5.9 per cent having no perception of light; 17.1 per cent, only perception of light; 36.4 per cent being able to perceive hand movement, and the remainder having some less severe impairment of vision. Facts on degree of visual loss are not given separately for the various causes of blindness. The major facts on the diabetic blind are summarized in Tables 5 to 7.

As Table 5 indicates, the number of new cases of blindness increased over the three-year period both for total cases and for diabetics. In part, this reflects the more frequent certification of cases still having a small degree of vision. The increase was relatively greater for diabetics than for all cases. The proportion of cases of blindness due to diabetes rose from 3.4 per cent of the total in 1948 to 4.9 per cent in 1950. Among females both the proportion and the total number of cases of blindness was greater than among males. The difference was particularly marked for blindness due to diabetes, with females outnumbering males by more than 3 to 1.

*Diabetes was involved in only 0.4 per cent of the cases with blindness due to a different cause in each eye.

TABLE 5

Number of reported cases of blindness in both eyes and number and per cent due to diabetes, by sex and calendar years: England, 1948-1950

	Both Sexes			Males			Females		
Year	All causes	Diabetes	Per cent	All causes	Diabetes	Per cent	All causes	Diabetes	Per cent
1948-1950	18150	775	4.3	7190	180	2.5	10960	595	5.4
1950	7647	376	4.9	2990	79	2.6	4657	297	6.4
1949	6987	279	4.0	2763	67	2.4	4224	212	5.0
1948	3516	120	3.4	1437	34	2.4	2079	86	4.1

Source: *The Causes of Blindness in England, 1948-1950,* by Arnold Sorsby, Ministry of Health, London, 1953.

TABLE 6

Age distribution of reported cases of blindness in both eyes and number and per cent due to diabetes: England, 1948-1950

Age periods (at registration)	Number		Per cent	
	Total blind	Total due to diabetes	Diabetes of total blind	Diabetics of specified age of total diabetes*
All ages	18150	775	4.3	
Total, known ages	17549	739	4.2	100.0
Under 20	616	0	—	—
20-29	283	10	3.5	1.4
30-39	456	24	5.3	3.2
40-49	786	42	5.3	5.7
50-59	1478	100	6.8	13.5
60-69	3198	291	9.1	39.4
70 & over	10732	272	2.5	36.8
Unknown	601	36	6.0	

*Of known age.

Source: *The Causes of Blindness in England, 1948-1950,* by Arnold Sorsby, Ministry of Health, London, 1953.

TABLE 7

Diabetes as a cause of blindness in both eyes, number reported and per cent distribution according to condition causing blindness. By sex: England, 1948-1950

	Both Sexes		Males		Females	
	Number	Per cent of total	Number	Per cent of total	Number	Per cent of total
All Conditions	775	100.0	180	100.0	595	100.0
Retinopathy	677	87.4	148	82.2	529	88.9
Eyeball	82	10.6	27	15.0	55	9.2
Other	16	2.1	5	2.8	11	1.8

Source: *The Causes of Blindness in England, 1948-1950,* by Arnold Sorsby, Ministry of Health, London, 1953.

The proportion of cases of blindness due to diabetes increased fairly steadily with age to a peak of 9.1 per cent of the total at ages 60 to 69. In the age group, 70 and over, the proportion fell sharply to 2.5 per cent of the total number (see Table 6).

Nevertheless, more than one-third of the cases of blindness due to diabetes were recorded at ages 70 and over, while nearly 40 per cent additional were between ages 60 and 69. No cases were reported under age 20, and 10, or 1.4 per cent of the total, were between ages 20 to 29.

Retinopathy was the predominant cause of blindness due to diabetes, accounting for about 7 out of 8 cases for both sexes combined (see Table 7). The proportion with retinopathy was appreciably higher in females than in males.

ABSTRACTS

Albanese, Anthony A.; Higgons, Reginald A.; Orto, Louise; Belmont, Aurora; and DiLallo, Rosemarie (*St. Luke's Hosp., New York, N. Y.*: EFFECT OF AGE ON THE UTILIZATION OF VARIOUS CARBOHYDRATES BY MAN. Metabolism 3:154-59, March 1954.

Subjects, aged 5 to 89 years, after a 12-hour fast were given 1 gm. of different sugars per kilo, and blood sugar tests were made at 0, ½, 1, 2 and 3 hours after sugar ingestion. Urinary sugar loss was also estimated. The rate of utilization in descending order was found to be fructose, invert sugar, sucrose, lactose, glucose; whereas dextrose utilization decreased markedly with age, fructose was only slightly affected.

Allen, O. P. (*Peoples Hosp., Akron, Ohio*): ARTERIOSCLEROSIS AND HEREDITY IN THE DIABETIC. Ohio Med. J., 49:991-93, November 1953.

The author relates the development of arteriosclerosis in the diabetic to hereditary factors and the damage done by various injuries such as "toxemias," acidosis, and "stress." No original data are presented.

Alvarez, Walter C. (*Minneapolis, Minn.*): HYPERGLYCEMIC GLYCOGENOLYTIC FACTOR OF THE PANCREAS. Mod. Med. 21:77-78, November 15, 1953.

For years physiologists have puzzled over many peculiar things about diabetes and insulin. For instance, total removal of the pancreas in man does not produce as severe a diabetes as often comes spontaneously. Also, there is something in ordinary insulin preparations which causes a preliminary rise in blood sugar. This is now called glucagon or the hyperglycemic-glycogenolytic factor of the pancreas. It is a polypeptide similar to insulin, but in some ways different. It counteracts the effects of insulin much as adrenalin does, but in chemical structure it differs greatly from adrenalin. Its production is stimulated by a growth hormone in the pituitary gland, and this throws additional light on the long-known relation between the pituitary and diabetes. As one might expect, alloxan, which destroys the beta cells, does not destroy the alpha cells and hence does not affect the secretion of glucagon. The giving of cobalt will, to some extent, knock out the alpha cells but does not destroy them entirely.

In 1950, McQuarrie and his colleagues at the University of Minnesota described the occurrence in children of certain families of a peculiar type of hyperglycemia during the first month of life. This condition responded to treatment with ACTH and was found to be associated with a total or almost total absence of the alpha cells in the pancreatic islands.

Evidently, then, physicians must now recognize a new gland of internal secretion with a new disease due to the failure of development of the gland. We can now suggest why a man who has to part with all his pancreas will not have as severe diabetes as has a man who has lost only his beta cells. With a pancreatectomy, the man loses both his insulin and his glucagon.

Amatuzio, Donald S.; Schultz, Alvin L.; Vanderbilt, Muriel J.; Rames, Eugene D.; and Nesbitt, Samuel (*Dept. of Med., V. A. Hosp., Univ. of Minnesota Med. Sch., Minneapolis, Minn.*): THE EFFECT OF EPINEPHRINE, INSULIN, AND HYPERTHYROIDISM ON THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST. J. Clin. Investigation 33:97-102, January 1954.

The disappearance rate of glucose in 17 normal men during the rapid intravenous glucose tolerance test was found to decrease after the administration of epinephrine. Insulin increased the rate of disappearance of glucose twofold to threefold in 18 normal men. In 15 of 17 subjects with hyperthyroidism, the rate of glucose disappearance was found to be normal or increased. After remission of the hyperthyroidism, the rate of disappearance of glucose was slower in eight, unchanged in five, and slightly more rapid in two patients.

The oral glucose tolerance curves in 6 of 16 patients with hyperthyroidism were interpreted as diabetic in type. Of the six patients who had diabetic-like curves before treatment, only four became normal after remission of the hyperthyroidism. Of the 10 patients with normal oral glucose tolerance curves before treatment, two became diabetic-like after therapy.

There was no correlation in the hyperthyroid group between the glucose disappearance rate and the oral glucose tolerance test before or after treatment.

Bacchus, Habeeb; and Heiffer, Melvin H. (*Dept. of Physiol., The George Washington Univ. Sch. of Med., Washington, D. C.*): CARBOHYDRATE METABOLISM IN ASCORBIC ACID DEFICIENCY. Am. J. Physiol. *176*:262-66, February 1954.

The nature of the disturbance of carbohydrate metabolism in ascorbic acid deficiency was studied in guinea pigs. Insulin tolerance tests on ascorbic-acid-deficient and control guinea pigs indicated that a progressive resistance to the hypoglycemic action of insulin accompanies ascorbic acid deficiency. Glucose-insulin tolerance tests confirmed the above findings. Glucose-insulin tolerance tests were conducted on ascorbic-acid-deficient and control adrenalectomized guinea pigs in order to ascertain whether the disturbance is ascribable to adrenal hyperactivity. The data demonstrate that the ascorbic-acid-deficient adrenalectomized guinea pig, like the intact (i.e., nonadrenalectomized) deficient guinea pig, is resistant to the hypoglycemic action of insulin. The carbohydrate-utilization technic of Cori and Cori was employed in a small series of animals. The data indicated that glycogenesis is disturbed in ascorbic acid deficiency.

The data are interpreted to indicate that the disturbance of carbohydrate metabolism occurring in ascorbic acid deficiency is (a) probably not due to diminished insulin secretion, since exogenous insulin failed to correct the disturbance, and (b) is probably not ascribable to adrenal hyperactivity, since the insulin resistance is observed even in ascorbic-acid-deficient adrenalectomized guinea pigs. Whether there is an associated diminution of glycolysis occurring in ascorbic acid deficiency remains to be ascertained.

Bedrossian, Robert H.; Pocock, Dean S.; Harvey, Wells F., Jr.; and Sindoni, Anthony S. (*Philadelphia Gen'l. Hosp., Philadelphia, Pa.*): DIABETIC RETINOPATHY TREATED WITH TESTOSTERONE. A.M.A. Arch. Ophth. 50:277-81, September 1953.

Hormone therapy with testosterone propionate or testosterone propionate and estradiol in weekly intramuscular injections, given for five months under the conditions of this study, was not demonstrably more effective in the control of diabetic retinopathy than were weekly injections of saline. The data indicate that weight, race, duration of diabetes, and type of insulin did not affect the results of treatment. The effects of the patient's age and the insulin dose were equivocal.

Benton, Paul C. (*Tulsa, Okla.*): THE EMOTIONAL ASPECTS OF DIABETES MELLITUS. J. Oklahoma M. A. *46*:295-300, November 1953.

Diabetes mellitus may be altered in respect to onset and course by the emotional state of the individual. Emotional factors require evaluation in treatment. The proper psychological emphasis may spell the difference between successful or unsuccessful management. One must treat the individual and not just his diabetes. Consideration of this aspect is as important as diet, urinalysis, and insulin injections.

Bera, G. N. (*Dept. of Physiol., Presidency Coll., Calcutta, India*): EFFECTS OF NIACIN AND NIACINAMIDE ON BLOOD SUGAR. Am. J. Physiol. *175*:296-98, November 1953.

Niacin and niacinamide, injected intramuscularly into fasted rabbits, with or without glucose, caused a distinct rise in blood sugar in each case reaching a maximum about 1 hour after injection. At this time the average niacin content of the blood was also found to be maximal.

These effects are similar to that of adrenalin on blood sugar, and it was found that the adrenalin content of the blood of these rabbits at the period when its niacin content was high was also maximal.

It is concluded that niacin or its amide on intramuscular injection provokes the secretion of adrenalin, which is very high when the niacin content of the blood is also very high. It produces thereby hyperglycemia, which is also very intense when the average niacin content is of high value and is responsible for the action of such niacinized blood on heart beats, blood vessels, and blood pressure.

Black, K. O.; Hosford, J. P.; Corbett, R. S.; and Turner, J. W. Aldren (*Depts. of Med., Surg., and Neurol., St. Bartholomew's Hosp., London*): SPONTANEOUS HYPERINSULINISM DUE TO ISLET-CELL ADENOMA. Brit. M. J. *1*:55-60, January 9, 1954.

Three cases of spontaneous hyperinsulinism due to islet-cell adenoma are described. All were in the third decade of life. Growth hormone was successfully used in one to assist in maintaining normoglycemia during weight reduction.

Bloom, Walter Lyon; and Wilhelmi, Alfred E. (*Dept. of Biochemistry and the Dept. of Med., Emory Univ., Sch. of Med., Emory Univ., Ga.*): DEXTRAN AS A SOURCE OF LIVER GLYCOGEN AND BLOOD REDUCING SUBSTANCE. Proc. Soc. Exp. Biol. & Med. *81*:501-03, November 1952.

In both rat and man, the oral administration of dextran leads to a significant and sustained increase in blood-reducing substance, most of which is fermentable. In the rat, this increase in blood sugar is accompanied by a significant increase in liver glycogen four hours after feeding. Dextran is therefore capable of being broken down in the intestine to products which yield glucose and glycogen in the animal. The early increase in blood sugar in both rat and man indicates that the intestinal breakdown of dextran may be a relatively rapid process, and it suggests that this may not be ascribable merely to bacterial action but more probably to an action of an enzyme or enzymes of the intestinal tract. Experiments now under way in this laboratory indicate that the latter possibility may be realized; suspensions of rat duodenal mucosa have been found to liberate glucose from dextran at rates which can account satisfactorily for the increases in blood sugar seen after feeding.

Bolinger, Robert E.; Grady, Harold J.; and Slinker, Betty J. (*Metabolism Sect., Univ. of Kansas Sch. of Med., Kansas City, Kan.*): THE EFFECT OF INJECTED HEPARIN ON THE ELECTROPHORESIS OF THE LIPOPROTEINS IN PATIENTS WITH HYPERCHOLESTEROLEMIA. Am. J. M. Sc. *227*:193-200, February 1954.

The effect of injected heparin on the electrophoretic pattern of the lipoprotein was studied in four patients with hypercholesterolemia and two normal individuals, using the method of paper electrophoresis.

In the pathological cases, the cholesterol and phospholipid values determined on the whole serum fell following the injection of heparin.

In two of the pathological cases, the cholesterol values as obtained by integration of the values from the paper strips decreased, and in two the values increased; in the case of the phospholipids, the values increased after heparin injections.

There was a change in all cases in the electrophoretic pattern of the lipids, with a blunting of the beta globulin lipid peaks, a shift of the peaks toward the alpha region, and an increase in the alpha globulin lipid peaks.

These studies are consistent with the hypothesis that cholesterol and phospholipid enter the protein-bound lipid phase from a free lipid phase under the influence of injected heparin.

Brodwall, Sverre; Skulstad, Aasmund; and Sagberg, Anne Elisabeth (*Bergen Univ., Neevengaarden Mental Hosp., Bergen, Norway*): COMPLICATIONS RESULTING FROM PROTRACTED INSULIN COMA. J. Clin. & Exper. Psychopath. *14*:184-88, December 1953.

Of 276 cases treated with insulin shock therapy at Neevengaarden Mental Hospital, serious complications occurred in only five cases. In these five patients, of whom four were pyknics, there was no correspondence between the duration and depth of the coma and the degree of the resulting defect. The first patient remained in a coma for 16 days, followed by considerable mental improvement. There were no signs of brain lesions afterward. The second patient was in a coma for five days. He remained in a state of physical and mental deterioration. Clinical symptoms indicate lesions in the brain cortex and the basal ganglia. The third patient was comatose for 10 minutes, followed by a period of confusion. Afterwards, there was a greater frequency of depressive periods and increased irritability plus permanent slight left-side lesions of the pyramidal tract. The fourth case of protracted coma was unusual because the patient suffered from convulsions when conscious and was able to answer simple questions. As in earlier reported cases, her blood sugar level remained normal during days of coma. How far her abnormal reaction to insulin may be considered a result of changes that had taken place in her brain as a result of frontal leucotomy remains an unanswered question. Since epileptic fits after this operation are not uncommon, it is possible that an acquired irritability may play a part. The fifth case, which also deserves special attention, concerns a patient who after given a relatively moderate dose of insulin turned from deep depression into a sudden manic state, although it was of only a few days' duration.

Campbell, James; Chaikof, L.; and Davidson, I. W. F. (*Dept. of Physiol., Univ. of Toronto, Toronto, Canada*): METAHYPOPHYSEAL DIABETES PRODUCED BY GROWTH HORMONE. Endocrinology *54*:48-58, January 1954.

Permanent diabetes of up to the 400 days' duration of the study was produced in dogs by the injection over 3 to 37 days of growth hormone prepared accord-

ing to the method of Wilhemi, Fishman, and Russell from Fraction A and by methods devised by the authors. The diabetes was as severe as that found in pancreatectomized dogs but is better tolerated, as demonstrated by the ability of some dogs to live for up to 150 days without exogenous insulin administration as contrasted to about 7 to 12 days for depancreatectomized dogs. Marked improvement was noted on insulin, however. Pancreatectomy of the metahypophyseal diabetic dogs did not significantly alter insulin requirements. Whereas the pancreatic acinar tissue of these dogs is normal histologically, the islet tissue is reduced, and the beta cells show severe degeneration. Extractable insulin from these pancreases is very low.

Caren, Raymond; and Morton, M. E. (*Radioisotope Unit, V. A. Hosp., Long Beach, and the Dept. of Med. and Biophysics, Sch. of Med., Univ. of California, Los Angeles, Calif.*): PYRIMIDINE METABOLISM IN DIABETES MELLITUS STUDIED WITH N^{15} LABELED URACIL. Am. J. M. Sc. 227:141-48, February 1954.

The authors advance the hypothesis that diabetes mellitus may result as an error of pyrimidine metabolism which produces an alloxan-type substance at the isodialuric stage of the degradation of uracil. This would in turn affect the insulin-producing cells of the pancreas to cause diabetes.

The pyrimidine uracil was synthesized with isotopic heavy nitrogen (N^{15}) and administered intravenously to a diabetic who did not receive insulin during the course of the study. The metabolism of the uracil was compared with a similar previous study in a normal man. It was shown that the uracil was broken down much more rapidly to urea in the diabetic than in the normal. However, only about 50 per cent of the administered N^{15} was recovered from the urine in both cases in the 72-hour period of investigation. An unidentified substance containing N^{15} was excreted by the diabetic for a much longer period of time (24 hours as compared to 8 hours for the normal). The urinary ammonia of the diabetic was found to contain the largest atom per cent excess of N^{15} in the nitrogenous compounds which were identified in the urine.

The authors discuss relation of the results of this study to the above hypothesis and also the possibility that uracil is broken down to urea by more than one route, whereby more end products than urea and ammonia are produced.

Cavallero, Cesare (*Institut d'Anatomie Pathologique de l' Université de Milan*): STUDIES ON THE HYPERGLYCEMIC FACTOR (GLUCAGON) OF THE PANCREAS. Revue Canadienne de biologie 12:509-29, December 1953.

From the results obtained by the author, it seems likely that the production of glucagon is under the control of the hypophyseal growth hormone. It was observed that the treatment of intact rats with different growth hormone preparations increased sharply the mitotic sensitivity of the pancreatic alpha-cells to colchicine; in other experiments the treatment of pituitary dwarf mice with growth hormone resulted in hypertrophic and hyperplastic changes of the islets associated with a high number of alpha-cells. From these latter experiments it was concluded that glucagon could be of no little importance in the normal process of growth.

Cone, Thomas E., Jr. (*Pediat. Serv. of the U. S. Naval Hosp., Bethesda, Md.*): DIABETES MELLITUS IN A MONGOLOID. J. M. Soc. New Jersey 51:66-67, February 1954.

The case of a child with mongolism and diabetes mellitus is presented, the first report of these two conditions occurring concomitantly.

Coon, William W.; Hodgson, Paul E.; and Hinerman, D. L. (*Depts. of Surg. and Pathology, Univ. of Michigan, Ann Arbor, Mich.*): FUNDAMENTAL PROBLEMS IN JET INJECTIONS. Am. J. M. Sc. 227:39-45, January 1954.

A study was made of the gross and microscopic pathological changes produced by jet injection as compared with needle injection of fluids for subcutaneous administration. No significant difference in the rate of absorption between the two methods was noted. However, injection by means of the jet syringe produced definite tissue damage, which, in part, proved to be irreversible; consequently, it was concluded that the jet syringe employed was unsafe for clinical use.

Darragh, J. H.; Womersley, R. A.; and Meroney, W. H. (*Dept. of Int. Med., Yale Univ. Sch. of Med., New Haven, Conn.*): FRUCTOSE IN THE TREATMENT OF DIABETIC KETOSIS. J. Clin. Investigation 32:1214-21, December 1953.

Fructose disappears rapidly from the blood in patients with diabetic ketosis, with or without insulin, and at the same rate as in normal subjects. By use of fructose instead of glucose, together with adequate amounts of insulin, carbohydrate can be administered early in the course of treatment of diabetic ketosis without increase in the effective osmotic pressure of the extracellular fluid. The dehydration associated with diabetic ketosis can be corrected rapidly by infusion of a hypotonic electrolyte solution made up to isotonicity with fructose. Intracellular water is increased early in the course of treatment.

Daughaday, William H., and Larner, J. (*Washington Univ. Sch. of Med. and Barnes and Homer Phillips Hosps. St. Louis, Mo.*): THE RENAL EXCRETION OF INOSITOL IN NORMAL AND DIABETIC HUMAN BEINGS. J. Clin. Investigation *33*:326-32, March 1954.

The urine of 11 nondiabetic subjects contained an average of 37 mg. of inositol per day (range 8 to 144 mg.). Urine volume correlated poorly with inositol excretion. Seven uncontrolled diabetic patients had a urinary excretion of from 280 to 851 mg. per day of inositol. The inosituria of diabetes disappeared after the control of glycosuria. Diabetic subjects excreted three times more inositol in their urine than did nondiabetic subjects following the slow intravenous administration of 20 mg. per kg. of inositol, but the levels of plasma dialyzable inositol were the same in the two groups.

It is concluded that a renal tubular mechanism for the reabsorption of inositol exists and that tubular transport of inositol is inhibited by high glucose loads. The inosituria of diabetes mellitus can be attributed to an increased inositol clearance produced by glycosuria and not by polyuria.

Dury, Abraham (*Dorn Lab. for Med. Res., Bradford Hosp., Bradford, Penn.*): MECHANISMS OF INSULIN AND EPINEPHRINE EFFECT ON THE LEVEL OF PLASMA POTASSIUM. Endocrinology *53*:564-71, November 1953.

Alloxanized-adrenalectomized groups of rats given maintaining injections of Lipo-adrenal extract were used in an attempt to elucidate the mechanism of actions of insulin and epinephrine on the level of plasma potassium.

The results showed that insulin administration induced a significant decrease in the level of plasma potassium only when a large exogenous supply of glucose was made available. It was shown that insulin administration does not induce a lowered plasma potassium level in the alloxanized-adrenalectomized rat just as was demonstrated in previous studies from this laboratory that it was incapable of effecting this change in the adrenalectomized or the adrenalenucleated rat. The results indicated that the effect of insulin on plasma potassium was in association with carbohydrate utilization. Epinephrine induced a lowered plasma potassium level in this type of animal without glucose infusion as well as in the group given the glucose solution. These results conform with those of other studies in the intact, adrenalectomized, and adrenalenucleated rat. The mechanism of action of epinephrine on the plasma potassium level could not be deduced, however, from the present data. The fact that epinephrine does induce this change in such a variety of conditions was considered evidence of its having an integral role in the mechanism of potassium homeostasis.

Editorial: FRUCTOSE AND INVERT SUGAR VERSUS GLUCOSE. Nutrition Rev. *11*:299-301, October 1953.

Urinary loss of glucose in nondiabetic subjects was slightly greater than that of fructose when administered at a rate of 0.5 gm. hexose per kg. per hour. The utilization of glucose by the liver of rats fasted 72 hours was decreased by 50 per cent but no significant change was found with fructose. Irrespective of urinary wastage and the transient problem of "starvation diabetes," the advantages from the standpoint of caloric intake are negligible.

Editorial: METABOLIC BLOCKS IN DIABETES. Nutrition Rev. *11*:312-14, October 1953.

Liver slices from diabetic rats incubated with C^{14} labeled glucose showed markedly reduced carbon-dioxide formation and almost total abolition of fatty acid synthesis. When C^{14} labeled fructose was used, the carbon-dioxide formation was the same from normal and diabetic livers, but the fatty acid synthesis was markedly reduced. This paper suggests that absence of insulin reduces the phosphorylation of glucose to glucose-6-phosphate, since it was shown that phosphohexose-isomerase activities of normal and diabetic liver were identical.

High fructose feeding restores the ability of diabetic

liver slices to convert acetate to fatty acids, and this apparent block is a secondary effect of a block in glucose utilization rather than a primary effect due to lack of insulin.

Editorial (*Birmingham, Ala.*): "SOLOX" POISONING. South. M.J. 47:281, March 1954.

During the past few years there have been several reports on intoxication resulting from ingestion of a denatured alcohol solvent, sold under the trade name Solox. The contents of this solvent include ethyl and methyl alcohol together with gasoline.

The clinical picture is one of alcoholic intoxication, coma, and in some cases eventual blindness. A consistent finding in the syndrome has been profound acidosis and *hypoglycemia.* The average blood sugar determination found in a series of these individuals was approximately 30 mg. per 100 cc. On physical examination, these individuals frequently present a bizarre neurological picture, consisting of various mental aberrations and almost always extension rigidity of all extremities.

Restorative treatment with glucose and electrolytes may result in prompt resumption of normal functions. With the possibility of prevention of blindness, mental deterioration, or even death, it is important that clinicians recognize this syndrome early and institute proper therapy. It should be suspected in all cases of alcoholic coma, especially those occurring in individuals in the low income bracket.

Editorials and Comments (*Chicago, Ill.*): OVERNUTRITION AND UNDERNUTRITION. J.A.M.A. *153*:1364, December 12, 1953.

That the effects of obesity are serious is amply supported by the statistics of insurance companies. The obese are poor surgical risks and are predisposed to hypertension, diabetes, and atherosclerosis.

It has been shown that in persons with a high serum cholesterol level, atherosclerosis develops at an earlier age than in persons with a normal or low level. On the basis of this observation, it was prematurely assumed in some quarters that the progress of atherosclerosis could be retarded by putting patients on a low-cholesterol diet. This now appears not to be true because both fats and cholesterol are readily synthesized in the body, and neither increasing nor decreasing the cholesterol in the diet appreciably affects the serum cholesterol level. On the other hand, it is true that this level increases with age and with gains in body weight. Walker has shown that, contrary to popular belief, there is a lowering of serum lipids with rapid weight loss even though liberal amounts of cholesterol are present in the diet. A nearly fat-free diet is not essential to rapid weight loss and may actually have a harmful effect on the body economy.

It may be concluded that any kind of diet that causes overweight will further atherosclerosis and that the best preventive measure is to remain at or slightly below the ideal weight. Even at full term, the offspring of a mother who is undernourished resemble those born prematurely. Undernourished children grow slowly as measured by height, weight, and "bone age." This slows their maturation and prolongs their life. Animal husbandmen have bred and fed their animals for rapid maturation.

Edwards, Sterling W. (*Dept. of Surg., Med. Coll. of Alabama, Birmingham, Ala.*): RECENT ADVANCES IN THE SURGERY OF OBLITERATIVE ARTERIAL DISEASES. J.M.A. Alabama *23*:125-28, November 1953.

The author reviews recent trends in the therapy of occlusive peripheral arteriosclerosis, stressing (a) the superiority of the development of collateral circulation, with maximal improvement requiring from 6 to 12 months to occur; (b) the value of either thromboendarterectomy or segmental arterectomy and vascular grafting in the management of segmental obstructive lesions producing intermittent claudication; and (c) the long-term satisfactory results obtained with conservative transmetatarsal and midcalf amputations for gangrene.

Fabrykant, Maximilian; and Ashe, Benjamin I. (*Dept. of Med. New York Univ. Post-graduate Med. Sch.*): NATURE AND PREVENTION OF LOCAL SKIN LESIONS FROM INSULIN ADMINISTRATION. OBSERVATIONS ON 100 PATIENTS. Metabolism *3*:1-10, January 1954.

One hundred diabetics treated with insulin for 2 months or more and living in all sociological and financial strata were examined and questioned at 2 to 6-week intervals during a 10-month period regarding the occurrence of skin lesions classified into 3 types. These were (1) in-

flammatory lesions, with itching, burning, tenderness, and swelling, appearing in a few minutes to 12 hours and subsiding in 1 to 7 days, (2) painless subcutaneous indurations developing in areas of repeated use and persisting for weeks or months, and (3) (a) atrophies with loss of fat covered by insensitive and often adherent skin and (b) hypertrophies of painless tumefactions covered with thick movable skin. Four injection technics were recognized: (a) conventional, folding of skin and slant angle injection, (b) fold-straight, with injection made perpendicular to skin, (c) automatic injector, (d) recommended, with needle inserted perpendicular to stretched skin. No description of needle length or depth of injection was given. Injection type a was associated with 29 per cent occasional and 50 per cent persistent lesions; type b, 10 per cent occasional and 20 per cent persistent; type c, 20 per cent occasional and 10 per cent persistent; and type d, 38 per cent occasional and no persistent lesions. Twenty-five per cent of all the patients were found to be consistently free of all lesions.

No relationship could be found to type of insulin, allergies, or interrupted insulin therapy. All evidence supported the view that such lesions represented nonspecific reactions to the mechanical and chemical irritation from repeated insulin injections. The frequency and persistence of such reactions can be reduced by proper technic.

Fawaz, George; and Fawaz, Eva N. (*Dept. of Pharmacol. Sch. of Med., American Univ. of Beirut, Beirut, Lebanon*): EFFECT OF METABOLITES ON ACCUMULATION OF CITRIC ACID IN FLUOROACETATE-POISONED RATS. Proc. Soc. Exper. Biol. & Med. *84*:680-84, December 1953.

In fluoroacetate-poisoned rats, the C_4 members of the Krebs cycle further increase the accumulation of citrate in the heart but not in the kidney. C_2 members in appropriate doses may completely overcome the fluoroacetate block, a finding which may be of significance in antidotal therapy. In nonpoisoned rats, both C_4 and C_2 members of the cycle increase the citrate level in the kidney.

Foreign Letters (*Brazil*): POSTPARTUM NECROSIS OF THE ANTERIOR HYPOPHYSIS. J.A.M.A. *153*:1376, December 12, 1953.

Four cases of panhypopituitarism resulting from postpartum ischemic necrosis of the anterior hypophysis are reported. In making their diagnoses, the authors used the basal metabolic rate and the serum cholesterol level to assay the thyroid function; the Robinson-Power-Kepler test, the response of the eosinophils to corticotropin (ACTH) and epinephrine, the tolerance to glucose and insulin, the blood sodium, potassium, and chloride levels, and the determination of the urinary 17-ketosteroids and corticoids to determine the suprarenal insufficiency; the colpocytology to ascertain the gonadal insufficiency in women; and the low urinary elimination of the gonadotropins to disclose the hypofunction secondary to a hypophyseal lesion.

Gault, Sidney D. (*Roscoe B. Jackson Memorial Lab., Bar Harbor, Me.*): THE EFFECT OF PAROTIDECTOMY ON BLOOD SUGAR LEVELS IN THE RAT AND MOUSE. J. Lab. & Clin. Med. *43*:119-22, January 1954.

A total bilateral parotidectomy was performed on rats and mice. There were no gross clinical changes noted and no symptoms attributable to hypoglycemia. Blood sugar determinations showed no significant alterations from the normal for each species. From the data presented, it does not appear that the parotid glands play any significant role in carbohydrate metabolism.

Geschwind, I. I.; and Staub, A. (*Dept. of Biochemistry (Hormone Res.), Univ. of California, Berkeley, and the Lilly Res. Labs., Indianapolis, Ind.*): LACK OF GROWTH-PROMOTING POTENCY AND OF TOXICITY OF GLUCAGON (HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR) IN HYPOPHYSECTOMIZED RATS. Proc. Soc. Exper. Biol. & Med. *84*:244-46, October 1953.

A highly purified preparation of glucagon in doses as high as 0.25 mg. per day had no effect on the width of the epiphyseal cartilage of the hypophysectomized rat as determined by the tibia test for growth hormone. Such a preparation possessed no toxicity when injected into these test animals.

Goldfarb, A. Robert; Santamaria, Leonida; and Foa, Piero P. (*Dept. of Biochemistry, Physiol., and Pharmacol., Chicago Med. Sch., Chicago, Ill.*): PHOSPHORUS METABOLISM IN THE DOG KIDNEY. Proc. Soc. Exper. Biol. & Med. *84*:523-28, December 1953.

P^{32} as sodium phosphate was injected into the intact

renal artery of dogs, while the blood emerging from the kidney was collected in a beaker by means of a venous cannula. The kidney was then removed and analyzed for the various fractions of phosphorus. It was found that P uptake by ADP-ATP and glucose-1-phosphate (G-1-P) was very rapid, more so in the cortex than in the medulla. It was concluded that G-1-P was derived from glycogen by the phosphorylase reaction. The very low relative specific activity of the glucose-6-phosphate (G-6-P) found in the kidney was formed elsewhere in the body and carried to this organ by the blood.

Goodman, Joseph I. (*Cleveland Heights, Ohio*): HEPATOMEGALY AND DIABETES MELLITUS. Ann. Int. Med. 39:1077-87, November 1953.

Four hundred and fifty-nine patients (319 males) separated into three groups of 379 controlled diabetics, 70 uncontrolled diabetics (24-hour glycosuria exceeding 50 gm.), and 10 keto-acidosis diabetics were examined for hepatomegaly. Hepatomegaly was more readily recognized by the author on percussion than palpation. He reported finding it present by this means in 9 per cent of the controlled diabetics, 60 per cent of the uncontrolled diabetics, and 100 per cent of the keto-acidotic diabetics.

Goodman, Joseph I. (*Cleveland Heights, Ohio*): REVIEW: INSULIN (HYPOGLYCEMIC) REACTIONS IN DIABETIC PATIENTS. Metabolism 2:485-99, November 1953.

Frostig, Himwich and their associates described the symptoms of insulin reactions in four groups, occurring in sequence.

The first group, appearing while the blood sugar is falling, consists of gradual depression of cerebral and cerebellar function, with lassitude, confusion, irritability, and restlessness, followed by hunger, dizziness, weakness, nervousness, tremor, and pallor and other signs of increased autonomic nervous system activity. Sometimes psychotic behavior also develops, finally stupor and coma or increased excitement, agitation, or delirium. The second group considered to be an expression of disturbed subcortical function is manifested by involuntary movements of a primitive type, such as sucking, grimacing, snarling, and athetosis, followed by myoclonic twitchings which, when forceful and generalized, are precursors of convulsions. Autonomic system manifestations may include periodic exophthalmos, dilated pupils, tachycardia, flushing, and salivation. The third symptom group is that of deepening coma, with tonic and torsional spasms, positive Babinski sign, dissociated eye movements, and decerebrate rigidity. The fourth or medullary stage begins with opisthotonos and is associated with parasympathetic signs of pinpoint, fixed pupils, bradycardia and finally loss of corneal and tendon reflexes just before death. Neurological changes of considerable or permanent duration may follow prolonged coma.

It is concluded that the mechanism of the neurological signs and symptoms due to hypoglycemia is similar to that associated with oxygen deficiency and Himwich has shown that the normal oxygen uptake by the brain is about 6.8 per cent of the oxygen from each 100 cc. of blood, while during hypoglycemic unconsciousness it removes only 2.6 vol. per cent of the oxygen. Carbohydrate is followed by rapid recovery and an oxygen uptake of 5.1 vol. per cent at the moment consciousness is regained.

The development of the definite pattern of hypoglycemic symptoms may depend upon differences in the metabolic rate in different parts of the brain. Variation is noted in the reported EEG abnormalities occurring in diabetics who are with and without hypoglycemia.

Anatomically, there are no absolutely characteristic changes in the brain as a result of severe hypoglycemia. The most common change noted is the finding of multiple petechial hemorrhages. Other changes in cases of severe hypoglycemia may consist of disappearance of brain cells, both gray and white matter, congestion, patchy demyelinization, encephalomalacia, active proliferation, cyst formation, and gliosis. Whereas pathologic findings of irreparable damage may occur with frequent severe insulin reactions, even mild hypoglycemia may produce petechial or larger hemorrhages. The author believes that insulin reactions should be avoided at all cost.

The author contends that the frequency and severity have markedly increased since the introduction of protamine insulin. He emphasizes the difficulties of subjective and objective recognition of the symptoms which occur when the blood sugar falls slowly, even when it reaches an extremely low level. In the light of the potential dangers inherent in hypoglycemia, he calls for greater efforts by physicians to avoid this pitfall in the treatment of diabetes.

Goodman, Joseph I. (*Mt. Sinai Hosp., Cleveland, Ohio*): VASCULAR LESIONS IN DIABETES MELLITUS: I. THE PATHOLOGIC AND CLINICAL ASPECTS OF ATHEROSCLEROSIS. Ohio M. J., *48*:1013-18, November 1952.

A short review is given of the literature relating to the pathologic and clinical aspects of atherosclerosis in diabetic patients.

Graham, Bruce D.; and Lowrey, George H. (*Dept. of Pediat. and Communicable Diseases, Univ. of Michigan, Ann Arbor*): CHEMICAL FINDINGS IN INFANTS BORN OF DIABETIC MOTHERS: A PRELIMINARY REPORT. Univ. Michigan M. Bull. *19*:267-72, October 1953.

Biochemical studies in infants born of diabetic parents showed that the infants had extremely variable plasma chloride and total base levels, and a high proportion had an uncompensated respiratory acidosis with a lowered *p*H, a condition rarely noted in normal newborn infants. The high plasma carbon-dioxide tension indicated that ventilatory control of this factor was lacking, the fault being either central or pulmonary. Furthermore, there appeared to be a direct correlation between the degree of acidosis and the severity of the abnormal clinical findings in general. The exact cause of this acidosis is not clear.

Guest, G. M. (*Children's Hosp. Res. Foundation and Dept. of Pediat., Univ. of Cincinnati Coll. of Med., Cincinnati, Ohio*): MANAGEMENT OF DIABETIC ACIDOSIS IN CHILDREN. Clin. Med. *61*:151-52, February 1954.

The sequence of therapy is, first, insulin in appropriate doses, preferably small. Repeated doses rather than initial large doses of several hundred units are preferred. There is evidence that insulin may be destroyed in the acidotic patient, or excreted; thus, repeated small doses give the promise of more effective continuous action. Next is the administration of salt solution in appropriate amounts to improve the circulation, followed by the administration of alkalies to bring the *p*H of the blood to normal, and, after the third or fourth hour, the administration of glucose in 5 per cent or even 10 per cent solution to accelerate glycogenesis. Most importance is attached to the role played by potassium in the postacidotic period. The great question is the size of the dose to be given. The amount must depend on the ability of the tissues to absorb it and the state of the patient with regard to previous depletion. Much research remains to be done on the indices which govern a rational plan of potassium dosage. In the meantime, it will be best to give minimal amounts, with careful observation of the electrocardiographic findings.

Hausberger, Franz X.; and Ramsay, Andrew J. (*Daniel Baugh Inst. of Anatomy of Jefferson Med. Coll. of Philadelphia, Philadelphia, Pa.*): STEROID DIABETES IN GUINEA PIGS: EFFECTS OF CORTISONE ADMINISTRATION ON BLOOD- AND URINARY GLUCOSE, NITROGEN EXCRETION, FAT DEPOSITION, AND THE ISLETS OF LANGERHANS. Endocrinology *53*:423-35, October 1953.

Male guinea pigs receiving 2.5 mg. of cortisone acetate daily show after several days a partial degranulation of the beta cells and a considerable hypertrophy of the islets. Ten to 50 mg. of cortisone daily produce in all animals an increased gain of body weight due to an augmented fat deposition, glucosuria and hyperglycemia. The nitrogen balance is positive, or only slightly negative. The islets of the pancreas show an extraordinary hypertrophy. The number and size of beta cells are considerably increased, and loss of the beta granulation takes place. If a severe diabetic condition is maintained for more than four weeks, a marked hydropic degeneration of many beta cells can be seen. After discontinuance of the cortisone administration, the body weight decreases due to loss of fat and the diabetes disappear slowly. The formerly enlarged and degranulated beta cells regain their normal size and appearance, but the severely hydropic beta cells do not recover.

Helmer, O. M.; and Root, Mary (*Lilly Research Labs., Indianapolis, Ind.*): THE EFFECT OF ACTH AND CORTISONE ON THE HYPERGLYCEMIC RESPONSE TO GLUCAGON. Endocrinology *54*:338-42, March 1954.

Glucagon (hyperglycemic-glycogenolytic factor) was administered intravenously to rabbits before and after treatment with ACTH or cortisone.

ACTH caused a 40-50 per cent increase in liver weight and glycogen content, and rabbits so treated showed a greater hyperglycemic response to glucagon.

The diabetogenic effect of cortisone was marked and greater than ACTH, and the high control blood sugar values may account for the failure of glucagon to show an enhanced action.

Since all rabbits show a hyperglycemic effect from glucagon after ACTH and since it was possible to distinguish between glucagon doses over a wide range, such treated rabbits might prove to be good test animals for glucagon assays.

Hendry, Edward B. (*Dept. of Biochemistry, Western Infirmary, Glasgow, Scotland*): DELAYED HEMOLYSIS OF HUMAN ERYTHROCYTES IN SOLUTIONS OF GLUCOSE. J. Gen. Physiol. 35:605-16, March 1952.

When erythrocytes are suspended in glucose solutions of concentrations ranging between 1.50 and 3.0 gm. per 100 cc., a delayed type of hemolysis occurs, consisting of a prolytic phase lasting about an hour followed by a hemolytic phase lasting about two hours. The system is especially sensitive to changes of *p*H and temperature, acidity and lowered temperatures prolonging the prolytic phase and slowing down the hemolytic phase. This type of hemolysis is inhibited by increased osmotic pressure and by phlorizin, but not by fluoride or iodoacetate. It is possible, but not yet proved, that delayed hemolysis in glucose solution is dependent on enzymic activity. Phosphorylation may be the limiting factor.

Hess, W. C.; and Shaffran, I. P. (*Dept. of Biological Chem., Georgetown Univ. Sch. of Med., Washington, D. C.*): RATE OF ABSORPTION AND FORMATION OF LIVER GLYCOGEN BY GLYCINE. Proc. Soc. Exper. Biol. & Med. 81:404-05, November 1952.

The rate of absorption of glycine from the gastrointestinal tract of the white rat was found to be 102 mg. per 100 gm. of body weight per hr. The rate did not vary significantly during absorption periods of from 0.5 to 3 hrs. Glycine is definitely glyconeogenic, reaching a peak of glycogen production 14 hours after its administration. A smaller, but definite, peak was observed at 1 hr.

Horvath, Steven M.; and Hamilton, Lyle H. (*Dept. of Physiol., Coll. of Med., State Univ. of Iowa, Iowa City, Iowa*): BLOOD CELL COUNT RESPONSE TO INFUSION OF POLYMERIC GLUCOSE. Am. J. Physiol. 176:319-21, February 1954.

The leucocyte and erythrocyte count was observed after an infusion of polymeric glucose to four dogs having normal blood volume, and two depleted by hemorrhage. There was a marked leucocytosis which was primarily due to an increase in both mononuclear and neutrophile cells. This increase was still evident 24 hours after infusion. Eosinophiles decreased early in the period following infusion, and none were seen in the 24-hour peripheral venous sample. The erythrocyte response did not reflect simple blood volume alterations but was probably complicated by a mobilization of cells from red cell depots.

Ingle, Dwight J. (*The Ben May Lab. for Cancer Res., Univ. of Chicago*): SOME STUDIES ON EXPERIMENTAL DIABETES; THE TENTH ANNUAL JOURNAL-LANCET LECTURE. Lancet 73:470-78, November 1953.

This paper is principally concerned with the effect of heteropoietic factors on carbohydrate metabolism. The word "heteropoietic" means "to cause differences." Although there are a number of methods of causing experimental animals to develop hyperglycemia and to waste glucose into the urine, it is doubtful that any form of experimental diabetes mellitus fully simulates the disease as it occurs in man. Among our studies of the effect of heteropoietic factors on experimental diabetes, we screen for compounds which will modify the diabetic state. Herein the experimenter tests this and that compound, more by random selection than by reason. It is a bit more tasteful to refer to the process as the courting of serendipity. Actually serendipity implies discovery of the unanticipated while pursuing another objective. In the practice of screening, the experimenter has no objective other than the chance observation of something worth-while. It is a useful procedure in the field of pharmacology, and there is no doubt that its continued practice in the field of carbohydrate metabolism will greatly extend the list of agents which will modify carbohydrate metabolism.

Ingle, Dwight J.; Beary, Dexter F.; and Purmalis, Andrejs (*Res. Labs., The Upjohn Co., Kalamazoo, Mich.*): COMPARISON OF THE EFFECT OF 11β-HYDROXYPROGESTERONE AND OF 11β, 17*a*-DIHYDROXYPROGESTERONE UPON THE GLYCOSURIA OF THE PARTIALLY DEPANCREATIZED RAT. Metabolism 2:510-12, November 1953.

Partially depancreatized force-fed rats were injected with doses up to 16 mg. per rat per day of 11β-hydroxy-

progesterone and of 11β, 17*a*-dihydroxyprogesterone. Both compounds cause exacerbation of the diabetes, and the latter compound is the more potent. This effect is manifest in either the presence or absence of the adrenal glands.

Ingle, Dwight J.; Beary, Dexter, F.; and Purmalis, Andrejs (*Res. Labs., The Upjohn Company, Kalamazoo, Mich.*): EFFECT OF ETHYLENEDIAMINE UPON GLYCOSURIA OF THE PARTIALLY DEPANCREATIZED RAT. Proc. Soc. Exper. Biol. & Med. *81*:3-4, October 1952.

The subcutaneous injection of ethylenediamine in ten partially depancreatized rats caused exacerbation of diabetes in each animal, but the glycosuria returned to the pre-injection level when the administration of the compound was stopped.

Jacobs, Sydney; Leonard, Alan J.; and Yager, Isadore (*Dept. of Med., Tulane Univ. Sch. of Med. and the Charity Hosp. of Louisiana at New Orleans, La.*): DIABETES AND TUBERCULOSIS. J.M.A. Georgia *42*:519-22, December 1953.

"Modhumelia (honey-urine) is a disease which the rich principally suffer from and is brought on by their own over-indulgence in rice, flour and sugar. The patient feels weak and emaciated and complains of frequent micturition, thirst and prostration. Ants flock around his urine. Carbuncles and phthsis are its frequent complications." This quotation from the *Ayur-Veda* of Susruta published in the year A.D. 600 suggests that even the ancient Hindus were aware that diabetes mellitus predisposes to pulmonary tuberculosis.

Many statistical studies indicate that tuberculosis follows diabetes because of some relationship between the two diseases and not by chance. Accordingly, tuberculosis is to be regarded as a complication of diabetes, in many respects more like vascular than suppurative states. Tuberculosis that develops in a diabetic is extremely grave. The age of onset is that of the diabetes rather than that of the tuberculosis, and the length of life after tuberculosis begins is limited. The life expectancy averaged 3.5 years after the development of tuberculosis in the authors' series.

John, Henry J. (*St. Luke's Hosp., Cleveland, Ohio*): DIETETIC MANAGEMENT OF DIABETES. Ohio M. J., *49*:994-97, November 1953.

The author summarizes his reasons for using a liberalized dietary regime for the management of diabetes mellitus.

Kadota, Ichiro; and Tokuyoshi, Abe (*Dept. of Pathology, Kyoto Univ. Sch. of Med., Kyoto, Japan*): CHEMICAL SPECIFICITY OF DIABETOGENIC ACTION OF QUINOLINE DERIVATIVES. J. Lab. & Clin. Med. *43*:375-85, March 1954.

The diabetogenic action of thirteen quinoline derivatives structurally related to 8-hydroxyquinoline was examined in rabbits. Close correlation between chemical structure and diabetogenic action in quinoline compounds has been established; 8-hydroxyquinaldine and 5-amino-8-hydroxyquinoline were confirmed to be diabetogenic, but 8-methoxyquinaldine was not. A hydroxy group in position 8 of quinoline was essential for diabetogenic action. The addition of hydroxy and carboxyl groups abolished the specific effect which was associated with a decrease in the toxicity. Since diabetogenic 8-hydroxyquinaldine and 5-amino-8-hydroxyquinoline have properties of an organic reagent, a close correlation between destructive action of the pancreatic islet cells and binding properties with metal ions was confirmed. The ability of these compounds to bind metal ions may explain their cytotoxic effect and thus their diabetogenic action.

Kahan, John (*Pharmacolog. Dept., Karolinska Inst., Stockholm 60, Sweden*): A RAPID PHOTOMETRIC METHOD FOR THE DETERMINATION OF GLYCOGEN. Arch. Biochem. *47*:408-18, December 1953.

The method for quantitative glycogen estimation in tissues such as liver, is based on the specific reaction of anthrone with glycogen. The procedure is performed directly on the trichloracetic acid tissue extract omitting the usual alkaline digestion, alcohol extraction, and acid hydrolysis. The method range is 2 to 300 micrograms of glycogen, with an experimental error for duplicates of ± 2.6 per cent.

Khattab, Mohamed; Flock, Eunice V.; Grindlay, John H.; and Bollman, Jesse L. (*Secs. of Biochemistry and of Surg. Res., Mayo Foundation and Mayo Clin., Rochester, Minn.*): HEPATIC INFLUENCE ON AMYLASE OF PLASMA. Am. J. Physiol. *175*:458-60, December 1953.

The amylase content of the plasma of dogs having extensive cirrhosis of the liver produced by repeated administration of carbon tetrachloride is similar to that of normal dogs. Blood of the portal, hepatic, and jugular veins simultaneously withdrawn has the same amylase content. Intravenous injection of pancreatic juice increases the amylase content of the plasma, and there is a slow removal of the excess amylase from the blood. Simultaneous determinations of amylase content of the blood from the portal, hepatic, and jugular veins during the time of elevated amylase content do not indicate destruction of amylase by the liver or intestine. Amylase from pancreatic juice secreted into the intestine does not appear in the blood of the portal vein in appreciable amounts.

Kinsell, Laurance W.; Balch, Harry E.; and Michaels, George D. (*Inst. for Metabolic Res. of the Highland Alameda Ct. Hosp., Oakland, Calif.*): MODIFICATION OF "STEROID DIABETES" BY POTASSIUM. Metabolism 2:421-23, September 1953.

Administration of large amounts of potassium to diabetic patients receiving intensive cortisone treatment (1) prevents resistance to insulin, and/or (2) increases sensitivity to insulin, and/or (3) increases production of insulin, and/or (4) diminishes the neoglucogenetic effect of cortisone. Because potassium depletion is a prominent feature of the metabolic effects of cortisone-like steroids, it seems probable that such depletion is in some measure responsible for the insulin resistance which has long been regarded as a characteristic of "steroid diabetes."

Kornblueth, Walter; Yardeni-Yaron, Elisheva; and Wertheimer, Ernst (*Dept. of Path. Physiol. of Hebrew Univ. Med. Sch., Jerusalem, Israel*): GLUCOSE UTILIZATION OF THE RETINA. II. INFLUENCE OF VARIOUS HORMONES ON THE GLUCOSE UTILIZATION OF THE RETINA. A.M.A. Arch. Ophth. 50:500-05, October 1953.

The results obtained in the authors' experiments clearly indicate that the glucose utilization of the retina is independent of the various hormones and hormonal deficiency states tested. These findings mark the retina as a unique tissue with regard to glucose metabolism. All other tissues, including the brain, may be altered by one or more of these hormones or endocrine deficiency states.

Krag, Cletus L. (*Div. of Chronic Diseases and Tuberculosis, U. S. Public Health Serv., Washington, D. C.*): THE PREVALENCE OF DIABETES MELLITUS AMONG THE AGED TESTED IN A COMMUNITY DIABETES PROGRAM. J. Gerontol. 8:324-27, July 1953.

Available data indicate that the prevalence of diabetes mellitus increases as age increases. The relative age-specific prevalence rates seem to be 0.5 per cent at 30 years of age, 4 to 5 per cent at 60 years of age, and 6 to 7 per cent at 70 years of age.

Kral, V. A.; and Smith, C. C. (*Verdun Protestant Hosp., Montreal, Canada*): REFLEXES IN INSULIN COMA. Arch. Neurol. & Psychiat. 70:713-21, December 1953.

The authors attempted to evaluate the depth of insulin subcoma and coma by following various reflexes normally present and the change in these reflexes as coma developed. They found that there was no specific sign or group of signs that could be relied upon as an indication of subcoma or coma. Only diminution or absence of the abdominal reflexes and fixation of the eyeballs were observed constantly in cases of full coma. In the investigation of three trigeminofacial reflexes, no essential difference could be found. It was felt that the loss of any one of these reflexes under hypoglycemic conditions should be taken as a sign of depressed function of the lower brain stem. These reflexes are, however, not constantly present in cases of full coma. Discussion of the theoretical implications of their findings followed.

Lawrence, R. D. (*London, W.1*): SEVEN INSULINS IN BRITAIN. British Medical Journal 2:1215, November 28, 1953.

Since Monday, November 16, seven insulin preparations have been available on the British market—three old and four completely new—to the medical profession and the diabetics of this country. The whole question of these new insulins was discussed by interested doctors at the annual meeting of the Diabetic Association last July, and it was felt more strongly that the introduction of all these little-known new preparations at once would be most confusing to doctors and, hence, even dangerous to patients. It was unanimously agreed to advise the authorities that one only, the least unknown and most generally promising, should be introduced first. This opinion was immediately forwarded both to the Ministry of Health and to the British Insulin Manufacturers.

Events have shown that this expert medical opinion has been completely ignored. Several diabetic centers have worked intensively at testing these new products for the British insulin manufacturers, and the neglect of our known opinion has been our reward.

Lee, Norman D.; and Williams, Robert H. (*Dept. of Med., Univ. of Washington Sch. of Med., Seattle, Wash.*): THE INTRACELLUAR LOCALIZATION OF LABELED THYROXINE AND LABELED INSULIN IN MAMMALIAN LIVER. Endocrinology *54*:5-19, January 1954.

When insulin-I^{131} or thyroxine-I^{131} is presented to the liver by blood, the hormone is actively concentrated by the liver with entry into the cytoplasm and fixation to the nucleus, and the different cytoplasmic fractions and the differences in distribution of the thyroxine-I^{131} among the cytostructural elements are different from that for insulin-I^{131}; these differences are maintained with respect to the time studies during the 60- to 120-minute interval.

Insulin localized in rat liver appears completely resistant to removal by perfusion whereas this technic removes a relatively large quantity of the localized thyroxine.

LeFevre, Paul G.; and LeFevre, Marian E. (*Dept. of Physiol. and Biophysics, Univ. of Vermont, Burlington, Vt.*): THE MECHANISM OF GLUCOSE TRANSFER INTO AND OUT OF THE HUMAN RED CELL. J. Gen. Physiol. *35*:891-907, July 20, 1952.

The kinetics of the movements of glucose in both directions across the surface of the human red cell were studied by optical recording of resultant cell volume changes. A wide experimental variety was arranged in the relations between the various quantitative factors contributing to the glucose gradient and the volume changes expected, in order to provide a maximum variety of systematic relations between those factors and the rate of glucose transfer. The kinetics were shown to follow the patterns predicted on the basis of a simple carrier system, involving formation of a highly dissociated complex between the sugar and some factor in the cell surface, provided the glucose concentrations used did not exceed about ¾ isosmotic. At very high glucose concentrations, this system apparently fails to operate; the failure is reversible upon lowering of the excessive glucose concentration.

Lestradet, H. (PARIS): HYPERGLYCEMIA WITHOUT GLYCOSURIA: PHYSIOPATHOLOGY AND TREATMENT. La presse médicale *61*:1482, November 14, 1953.

Hyperglycemia without glycosuria is a syndrome for which no explanation is to be found outside the classical ground of diabetes mellitus. It would be, indeed, difficult to admit that the supervention of some nephropathy would have made it possible again for the body cells to utilize the glucose, since the absence of insulin had theoretically suppressed the possibility for this utilization. On the contrary, if it were admitted, in accordance with most recent works, that in diabetics the glucose is normally utilized and that the basic disorder consists in a difficulty in penetration of the cell by glucose compensated by a reaction hyperglycemia, the physiopathology of hyperglycemia without glycosuria would not seem obscure.

The author believes that hyperglycemia without glycosuria points to a poor prognosis, because of a suspected association with a nephropathy. He recommends a diet high in carbohydrate and vitamins, relatively low in fats and proteins, and more or less restrictive in electrolytes, according to the balance findings. Treatment by insulin is logically recommended, with administration of such adjuvants as testosterone and vitamin B_{12}.

Lever, Walter F.; Smith, Peter A. J.; and Hurley, Nancy A. (*Dept. of Dermatology, Harvard Med. Sch., and Dermatologic Serv., Massachusetts Gen'l. Hosp., Boston*): EFFECTS OF INTRAVENOUS HEPARIN ON THE PLASMA LIPOPROTEINS IN PRIMARY HYPERCHOLESTEREMIC XANTHOMATOSIS AND IDIOPATHIC HYPERLIPEMIA. Science *118*:653-54, November 27, 1953.

The authors report upon electrophoretic and lipid analyses before and 15 minutes after intravenous injection of 50 mg. of heparin in 7 normal subjects, 8 patients with primary hypercholesteremic xanthomatosis, and 7 patients with idiopathic hyperlipemia.

There was no significant electrophoretic or lipid analytic change in 5 of the 7 normal subjects. In 2 the B-1 peak decreased with compensatory increase in either the A-1 and albumin or the A-2 peaks. In primary hypercholesteremic xanthomatosis, all 8 patients showed an abnormally high B-1 peak. After heparin, the B-1 peak decreased in 6 patients with compensatory increase in the A-2 peak in 3, in the albumin peak in 1, and in both the A-2 and albumin peaks in 2. The elevated cholesterol values decreased slightly in all 8

patients, without change in the neutral fats or phospholipids. In 6 patients with idiopathic hyperlipemia, the fasting electrophoretic pattern showed an abnormally high A-2 peak in 3 and both A-2 and B-1 peaks in 3. After heparin, the previously high peaks returned to normal size, and a new peak appeared ahead of the albumin peak.

Plasma protein fractionation by Cohn's method revealed that the elevations of the B-1 peak in xanthomatosis and of the A-2 and B-1 peaks in hyperlipemia were caused by a lipoprotein with the characteristics of B-1 lipoprotein. The increased speed of electrophoretic migration after heparin injection may be due either to combination with the highly negatively charged heparin or to decrease in particle size as a result of the lipolytic action of heparin.

Levine, Rachmiel; and Taubenhaus, Matthew (*Michael Reese Hosp., Chicago, Ill.*): CLINICAL CONFERENCE ON METABOLIC PROBLEMS: ESSENTIAL FRUCTOSURIA. Metabolism *3*:82-87, January 1954.

A case report is presented of a 35-year-old female with known fructosuria since age 8. Some discussion of the cause and effects and characteristics of the condition is given.

Lotspeich, William D.; and Petersen, Villy Posborg (*Dept. of Biochemistry, Univ. of Oxford, and Dept. of Physiol., Univ. of Cincinnati, Coll. of Med., Cincinnati, Ohio*): EFFECT OF ANTERIOR PITUITARY GROWTH HORMONE ON SYNTHESIS OF ACETOACETATE BY SURVIVING SLICES OF RAT LIVER. Am. J. Physiol. *176*: 232-38, February 1954.

A study was made of the effect of pretreatment with anterior pituitary growth hormone (GH) on the synthesis of acetoacetate by surviving slices of rat liver. It was found that the liver slices from the animals given growth hormone produced significantly greater quantities of acetoacetate than did slices from the isocalorically fed controls. There was also noted a marked and sudden depletion of liver glycogen as a result of growth hormone administration. These findings were repeatedly seen in fed rats receiving injections of growth hormone over several days or in 18- to 24-hour fasted rats two hours after a single injection. Further studies on the "single injection" rats showed that in two hours after administration of growth hormone there was hypoglycemia, ketonemia, and increased liver lipid content. These later findings were in agreement with similar observations of others.

It was suggested that the accelerated fat catabolism induced by growth hormone treatment might well be secondary to the depletion of liver glycogen, a sequence of events similar to those seen in other states where stores of liver glycogen are depleted. Such an explanation of the observed facts would place the biochemical site of action of growth hormone somewhere in the chain of reactions of glycogenolysis. It was further suggested that the ketosis and fatty liver of uncontrolled diabetes might be the result of an aberration in the normal synergism between growth hormone and insulin as they regulate the synthesis of new protein for tissue growth.

Lukens, F. D. W.; Spoont, Stanley; and Barol, Samuel R. (*Univ. of Pennsylvania Hosp., Philadelphia, Pa.*): TEACHING CLINIC. HYPOGLYCEMIA. J. Clin. Endocrinol. & Metab. *14*:248-54, February 1954.

A teaching clinic on hypoglycemia, with case presentations and discussions, is presented.

Mansour, Tag E.; and Hewitt, William F., Jr. (*Dept. of Physiol., Howard U. Sch. of Med., Washington, D.C.*): SENSITIVITY TO INSULIN DURING ADRENOCORTICAL RESPONSE TO COLD STRESS IN RATS. Endocrinology *54*:20-25, January 1954.

Adult rats were exposed to cold stress for one, six, or nine days continuously; blood sugar changes following the subcutaneous injection of insulin were measured before and after such stress, and the response of the adrenal glands in similarly stressed rats was determined by measurement of adrenal cholesterol, ascorbic acid, and the ratio of total adrenal weight to body weight.

Cold stress for one day produced no blood sugar change but did cause marked depletion of adrenal cholesterol and ascorbic acid. After six days of cold stress, there was hyperglycemia and hypersensitivity to insulin, and the adrenal showed signs of higher activity. After nine days, hyperglycemia and insulin hypersensitivity were still present, but the adrenal activity had returned to near normal levels.

Martin, Samuel P.; McKinney, Gordon R.; Green, R.; and Becker, Caroline (*Duke Univ. Sch. of Med. Dur-*

ham, N. C.): THE INFLUENCE OF GLUCOSE, FRUCTOSE, AND INSULIN ON THE METABOLISM OF LEUKOCYTES OF HEALTHY AND DIABETIC SUBJECTS. J. Clin. Investigation *32*:1171-74, November 1953.

Leukocytes from healthy individuals produce more lactic acid from glucose than from fructose, and fructose increases the glucose utilization. This difference is abolished by grinding the cells. Leukocytes from diabetic subjects produce more lactic acid from fructose than from glucose. In the healthy subject, insulin had no measured effect on the lactic production of the cell; but, in the diabetic, it produced a significant increase in lactate formation with glucose but not with fructose. The utilization of glucose was significantly increased by insulin in the diabetic group but not in the control group. Cell injury blocked the hormone effect.

Mason, A. Stuart; and Verel, D. (*London E.1.*): INSULIN ZINC SUSPENSIONS. British Medical Journal *2*: 1215-16, November 28, 1953.

There is no doubt that the new insulins, particularly lente, are a valuable addition to the range available for treating diabetes. The authors do not think that any one preparation can cover the whole range of the diabetic population; the other insulin preparations which are available have still a place in outpatient treatment.

Master, Arthur M.; Jaffe, Harry L.; and Chesky, Kenneth (*New York*): RELATIONSHIP OF OBESITY TO CORONARY DISEASE AND HYPERTENSION. J.A.M.A. *153*: 1499-1501, December 26, 1953.

The relation of obesity to heart disease is reviewed. The harmful influence of obesity on the normal and on the diseased heart is well established. Persons with heart disease or hypertension who are obese have a much higher mortality rate than those who are of average weight or below. The development of coronary disease and hypertension in women may not be influenced by obesity. Although obesity occurs more commonly in patients with hypertension or coronary disease, no definite conclusion concerning the etiological relationship between obesity and these diseases can be drawn. The reports in the literature and the authors' observations, however, clearly indicate the importance of avoiding obesity in cardiovascular disease.

Mayer, J.; and Jones, Anne K. (*Dept. of Nutrition, Harvard Sch. of Public Health, and the Dept. of Physiol., Harvard Med. Sch., Boston, Mass.*): HYPERCHOLESTEREMIA IN THE HEREDITARY OBESE-HYPERGLYCEMIC SYNDROME OF MICE. Am. J. Physiol. *175*:339-42, December 1953.

Hypercholesteremia is an integral part of the hereditary obese-hyperglycemic syndrome. At 4 or 5 months, serum cholesterol levels in the obese animals are double those characteristic of the nonobese littermates.

Cholesterol levels are further increased in the obese animals by 2-week treatment with high-protein and high-carbohydrate diets, by fasting and by growth hormone, and by decreased thyroxine. In the nonobese animals, ACTH and growth hormone increase and high-carbohydrate and high-protein diets and thyroxine lower cholesterol levels.

McCullagh, E. Perry; Skillern, Penn G.; and Schaffenburg, Carl A. (*Dept. of Endocrinology and Res. Div., Cleveland Clin.*): THE USE OF CORTISONE IN THE TREATMENT OF THE PANHYPOPITUITARISM DUE TO POSTPARTUM NECROSIS OF THE PITUITARY (SHEEHAN'S SYNDROME). Cleveland Clin. Quart. *21*:31-39, January 1954.

The clinical features and laboratory findings in two cases of panhypopituitarism due to postpartum necrosis of the pituitary gland have been presented. Multiple glandular replacement therapy, particularly cortisone, transformed the state of these women from one of chronic ill health to one of essentially normal health. In our second patient, cortisone not only relieved the systemic effects of adrenal insufficiency but also corrected a severe hypoglycemia. The use of cortisone or hydrocortisone in preference to corticotropin is advocated because they are more surely effective, more rapidly effective, and more easily administered.

McVay, Leon V., Jr.; Sprunt, Douglas H.; Stern, Thomas N.; Tatum, Frederick E.; and Lipscomb, Alys (*Div. of Med., Path., and Bact., Univ. of Tennessee Coll. of Med., and John Gaston Hosp., Memphis, Tenn.*): ANTIBIOTIC PREVENTION OF INTERCURRENT INFECTIONS IN DIABETES MELLITUS. Ann. Int. Med. *40*:269-84, February 1954.

Ninety-four patients given 250 mg. of aureomycin containing Paraben twice daily on an empty stomach were

compared with 95 similar patients given a placebo at the same times under the blind control method as to the incidence of respiratory infection, pyuria, and changes in subjective well-being over a 4- to 21-month period.

In the aureomycin-treated group, respiratory infections were reduced by 50 per cent or more in 51 cases, unchanged in 39, and increased in 4, with the control group showing a reduction in 20 cases, no change in 66, and more in 9.

Pyuria occurred less often in the aureomycin series than in the controls, but the difference was not significant.

In the aureomycin series, subjective opinions were in 63 cases better, no change in 29, and worse in 2; in the control series for the same groups, there were 28, 57, and 10 cases respectively.

Liver function and bone marrow preparations showed no changes of significance during the study.

Mendeloff, Albert I.; and Weichselbaum, Theodore E. (*Nutrition Res. Lab., Dept. of Preventive Med., the Dept. of Surg., Washington Univ. Sch. of Med. and Barnes Hosp., St. Louis, Mo.*): ROLE OF THE HUMAN LIVER IN THE ASSIMILATION OF INTRAVENOUSLY ADMINISTERED FRUCTOSE. Metabolism 2:450-58, September 1953.

In five normal unanesthetized human subjects, the role of the liver in the metabolism of intravenously administered fructose was investigated by the hepatic vein catheterization technic. The following conclusions were drawn from the data obtained: (a) The removal of fructose by the splanchnic bed accounted for 32 to 48 per cent of the amount of fructose infused. (b) During the fructose infusion, the liver produced lactic and pyruvic acids, which represented from 20 to 50 per cent of the fructose removed by the splanchnic bed.

Milch, Lawrence J.; Redmond, Robert F.; and Calhoun, William W. (*Dept. of Pharmacology and Biochemistry, U.S.A.F. Sch. of Aviation Med., Randolph Field, Tex.*): PLASMA LIPOPROTEIN CHANGES INDUCED BY ACUTE LOCAL COLD INJURY. Am. J. Med. Sci. 225:416-20, April 1953.

The authors report that, in rabbits subjected to acute local cold injury, highly significant increases were noted after 24 hours in plasma concentrations of cholesterol, of S_f 12-20, and of S_f 20-100 classes of lipoproteins. Little change was observed in either packed-cell volume or in plasma protein content after injury, so the lipoprotein increases were not due to hemoconcentration. A possible source of the increased lipoproteins is synthesis by the injured tissues as part of the reparative process. The rise in cholesterol may be related to reports of atherosclerosis after acute trauma, although this possibility presumably is minimized by the corresponding elevations in cholesterol and phospholipid levels, so that the cholesterol/phospholipid ratios are not changed.

Miller, Emery C.; and Marble, Alexander (*The Joslin Clin. and the Baker Clin. Res. Lab., New England Deaconess Hosp., Boston, Mass.*): DIABETES IN THE ELDERLY. J. Am. Geriatrics Soc. 1:755-62, November 1953.

An analysis of 2,114 hospital admissions of diabetic patients showed 22 per cent of these to have been persons 65 years of age or over. There were 184 patients 70 years or older. Among the 184 patients, there were twice as many females as males. The average duration of diabetes was twelve years; among 15 with onset under the age of 50, the duration of diabetes ranged from twenty-two to forty-four years. In only 46 patients was the onset of diabetes at age 70 or above. The daily insulin requirement of 61 per cent of the 184 patients was between 20 and 49 units daily. In 10 per cent it was 50 to 99 units, and 5 elderly patients required 100 or more units daily. Among complications, vascular disease was most common and most important. Arteriosclerotic heart disease was present in 57 per cent, peripheral vascular disease in 49 per cent, retinitis in 26 per cent, and hypertension in 55 per cent. Surgery was performed in 37 of the 184 patients, and in 27 of these, amputations were carried out.

Mosenthal, Herman O. (*889 Lexington Ave., New York 21, N. Y.*): CONTROL OF THE COMPLICATIONS OF DIABETES: HYPERGLYCEMIA AND GLYCOSURIA; ENDOGENOUS AND EXOGENOUS INSULIN. Am. J. M. Sc. 227:134-40, February 1954.

The author elaborates upon the hypothesis presented by Warren and Le Compte that diabetic complications in the retina, kidneys, heart, pancreas, and arteries result from abnormal glycogen deposition secondary to persistent hyperglycemia. He points out endogenous insulin first is carried to and predominantly bound by the

liver in distinction to injected insulin, which is distributed throughout the extrahepatic tissues; hence, the former more effectively limits postprandial hyperglycemia through stimulating more efficient hepatic activity. A mode of therapy is recommended which is designed to prevent inordinate postprandial rise of blood sugar by use of an insulin with prolonged action and a diet containing no free sugar and a regular amount of slowly absorbable sugar in the form of starches and, to a lesser extent, proteins.

Natelson, Robert P. (*Los Angeles, Calif.*): COEXISTENT ACROMEGALY, DIABETES MELLITUS AND DIABETES INSIPIDUS. Ann. Int. Med., *40*:788-97, April 1954.

A case with autopsy findings of an acromegalic with the extremely rare complication of coexistent diabetes mellitus and diabetes insipidus is reported. A brief historical review is presented of the occurrence of diabetes mellitus in the acromegalic, the coexistence of diabetes mellitus and diabetes insipidus, and the coexistence of acromegaly, diabetes mellitus, and diabetes insipidus. The pathogenesis of the development of diabetes mellitus and diabetes insipidus in the acromegalic is discussed.

Packard, D. R.; Beazlie, F. S., Jr.; and Creecy, A. A. (*Newport News, Va.*): UNUSUAL COMPLICATIONS IN DIABETES MELLITUS: CASE REPORT. Virginia M. Month. *80*:557-59, October 1953.

A case of diabetes mellitus with cystitis emphysematosa diagnosed antemortem is presented. In spite of intensive therapy, death occurred soon. At necropsy, necrotizing renal papillitis, cortical necrosis of the kidney, and a dissecting aneurysm of the left common iliac artery with massive retroperitoneal hemorrhage were found. These findings again demonstrate the need to be alert for unusual complications in individuals with diabetes mellitus and urinary tract infection and the value of post-mortem examinations in diabetics even though the cause of death may appear to be obvious.

Pincus, I. J.; and Rutman, J. Z. (*Jefferson Med. Coll., and Grad. Sch. of Med., Univ. of Pennsylvania, Philadelphia, Penn.*): GLUCAGON, THE HYPERGLYCEMIC AGENT IN PANCREATIC EXTRACTS; A POSSIBLE FACTOR IN CERTAIN TYPES OF DIABETES. A.M.A. Arch. Int. Med. *92*:666-77, November 1953.

Evidence has been presented that a substance, glucagon, which raises the blood sugar level, can be extracted from the pancreas and, furthermore, is probably secreted by the pancreas into the venous blood from the pancreas. This substance raises the blood sugar level by releasing glucose from hepatic glycogen and apparently acts as an adjunct rather than as an antagonist to insulin. It is suggested that the presence of this factor may modify the response of a patient to insulin and possibly to other regulating hormones and may account for some hitherto unexplained phenomena in the diabetic patient. Further study of the physiologic role of this factor is required.

Powell, R.; and Bradshaw, S. (*Med. Inf. Dept., Evans Med. Supplies, Ltd., Liverpool, England*): INSULIN ZINC SUSPENSIONS. British Medical Journal *2*:1216, November 28, 1953.

The authors quote conflicting opinions in regard to the introduction of insulin zinc suspensions—lente, semilente and ultra-lente. Careful trials have been and are being carried out with all three of these preparations in Denmark and in Britain, and the results appear to be favorable.

Queries and Minor Notes (*Riverside, Calif.*): BURNING SENSATION IN MOUTH. J.A.M.A. *153*:1498, December 19, 1953.

A burning sensation of the tongue and oral mucosa is relatively common and may be related to systemic disease, such as diabetes, vitamin A deficiencies, pernicious anemia, and decreases in salivary output. One of the changes closely connected with aging is dry mouth, associated with loss of keratinization of the mucosa and accompanied by stickiness of saliva that leads to mechanical irritation. The irritation may not cause gross changes in the mucosa. In some patients a burning sensation of the mucosa is psychologenic.

Queries and Minor Notes (*India*): GLUCOSE SOLUTION INTRAMUSCULARLY. J.A.M.A. *154*:100, January 2, 1954.

Glucose may be given intramuscularly in concentration up to 5 per cent without causing sloughing.

Queries and Minor Notes (*Bronx, New York*): IMPOTENCE IN DIABETICS. J.A.M.A. *153*:1066, November 14, 1953.

The mechanism of impotence in diabetes could be due to pathological changes in the sexual glands, to alteration of the secretion of the pituitary gland, or to dysfunction of one or the other on account of the diabetic state. Impotence occasionally accompanies the onset of diabetes, and usually there is no obvious disease or deformity in the genital tract. The condition appears to be functional rather than organic. Against its being of neuritic origin is its usual permanence, whereas with diabetic neuritis, peripheral or otherwise, improvement is almost invariable.

The incidence of impotence in diabetes is unknown, but it is a common symptom. Naunyn stated that, in men with diabetes, impotence is one of the most constant symptoms. Yet it can be absent, and, instead of it, there may be temporarily an increased sexual desire. Impotence may be a premonitory symptom. It is not always the consequence of exhaustion or loss of sugar in the urine, since it occurs in well-nourished diabetics with very little excretion of sugar. Sexual capability sometimes returns when glycosuria disappears or decreases, but this is exceptional in severe cases. Atrophy of the testicles has been observed in young men. Psychic factors such as anxiety and fear of the future with respect to vision, arteriosclerosis, and gangrene, have special importance in diabetic patients. Treatment is unsatisfactory but testosterone in 25 mg. doses injected twice weekly has occasionally produced surprising results.

Ricketts, H. T.; Petersen, E. S.; Tupikova, Natalia; and Steiner, Paul A. (*Univ. of Chicago Clin., Chicago, Ill.*): SPONTANEOUS DIABETES IN DOGS: AN ACCOUNT OF EIGHT CASES. J. Lab. & Clin. Med. *42*:937, December 1953. (Abstract from Proceedings of 26th Annual Meeting, Central Society for Clinical Research.)

Spontaneous canine diabetes was found to be characterized by the absence of recognizable beta cells in the islands of Langerhans and, when determined, an insulin content of the pancreas far below normal. In three cases with diabetes of brief duration, there was hydropic degeneration and in one of these glycogen was found within the islets. In one dog with glomerular lipidosis, the lesions closely resembled, but perhaps were not identical with, the spheroid bodies of intercapillary glomerulosclerosis in man.

Rippy, Edwin L. (*Dallas, Tex.*): DIABETES IN CHILDHOOD. Louisiana M. Soc. *105*:421-26, November 1953.

The child whom you have just found to have diabetes is literally dying. There are methods at your disposal which will save his life, but it will take a great deal of your time, your patience, and your knowledge. This will prove to be a relatively unremunerative case. For the next few days you will spend much time in altering this vicious sequence of events and in orientating the confused and disturbed parents, not to mention the tedious hours of instruction as you literally become the lifelong guardian of this child's physical and emotional development. If you do not wish to undertake this obligation, refer the child to someone who does.

Diabetic children are reared as all children should be. They must not be treated as afflicted children. They must be taught at an early date self-discipline and self-reliance. They tend to develop a sense of responsibility and to mature earlier than the average child. When well controlled, they are a healthy lot and tend to be above the average in general intelligence. The petted, spoiled, overprotected diabetic child will eventually destroy himself, since adulthood tends to separate him from parental protection. Actually, however, the diabetic child, if given half a chance, adapts himself amazingly well to his disorder much to the surprise of all concerned.

When treatment is first begun, it is best to use unmodified insulin "on demand" for the first few days. One may be surprised at how much insulin a child will need daily at the onset—80 units not being unusual, but the need decreases by the day. The extreme sensitivity of infants to insulin must be remembered, however, their dosage of insulin being calculated in tenths of a unit. As the insulin dosage appears to level off, one may change to NPH insulin, giving a total morning dose of approximately three-fourths the total amount of regular insulin given the last day. Children react badly to venupuncture, and blood sugar tests are of little value until glycosuria has been checked. The micromethod of blood sugar determinations are advantageous in children.

Most children may be well regulated on one morning dose of NPH insulin; awkward insulin schedules are to be avoided. During infection, regardless of appetite, the need for insulin almost invariably increases; and because of this fact, together with the uncertainty of constant food intake, it may be a good plan to discontinue modified insulin and return temporarily to "insulin on demand" as indicated by urine tests every four hours. Tests for ketonuria should also be made.

The author believes that there is no place in the life of a child diabetic for the so-called "free diet."

Rosecan, Marvin; and Daughaday, William H. (*Washington Univ. Sch. of Med., the Barnes Hosp., Homer G. Phillips Hosps., St. Louis, Mo.*): A COMPARISON OF INSULIN TREATMENT WITH AND WITHOUT ADDED CARBOHYDRATE IN HUMAN DIABETIC KETOSIS. J. Clin. Investigation *33*:49-56, January 1954.

The fall in the total blood ketones in diabetic acidosis during insulin therapy with and without the administration of carbohydrate has been measured. A direct comparison of methods of therapy was accomplished by inducing ketosis 20 times in eight diabetic patients.

The blood ketone levels fall more rapidly following the intravenous administration of glucose and fructose than following the administration of saline solution with no carbohydrate. There was no significant difference in the effect of glucose and fructose on the rate of fall of blood ketones but hyperglycemia was less prolonged and glycosuria was less in amount after intravenous fructose.

Rosenman, Ray H.; Byers, Sanford O.; and Friedman, Meyer (*Harold Brunn Inst., Mount Zion Hosp., San Francisco, Calif.*): ROLE OF CHOLATE IN DIETARY-INDUCED HYPERCHOLESTEREMIA OF RATS AND RABBITS. Am. J. Physiol. *175*:307-09, November 1953.

The present studies have confirmed the finding that marked chronic hypercholesteremia without atherosclerosis occurs in rats simultaneously fed cholesterol and cholate. Perhaps the nondevelopment of atherosclerosis is related to the associated rise of plasma phospholipids in these animals. The hypercholesteremia produced in rats and rabbits fed cholesterol, concentration cholate, or both together, is independent of the plasma cholate and is due to increased absorption of cholesterol. It is concluded that dietary-induced hypercholesteremia as well as the augmentative effect of feeding cholate is independent of the known 'intravascular' ability of cholate to induce hypercholesteremia.

Sacks, Jacob; and Sinex, Marott F. (*Biol. and Med. Depts., Brookhaven Nat'l. Lab., Upton, N. Y.*): INSULIN AND THE RELATION BETWEEN PHOSPHATE TRANSPORT AND GLUCOSE METABOLISM. Am. J. Physiol. *175*:353-57, December 1953.

The amount of C^{14} glucose converted to CO_2 and glycogen by rat diaphragm has been compared with the amount of P^{32} phosphate incorporated into ATP, phosphocreatine, and hexosemonophosphate. Insulin was found to increase the transport of phosphate into diaphragm by 50 per cent. The increases found were of the same order of magnitude for phosphocreatine P, the labile P of ATP, and hexosemonophosphate P. In confirmation of the findings of previous investigators, insulin was found to increase both the oxidation of glucose and the deposition of glycogen, without any effect on the oxygen consumption of the tissue. On a molar basis, the increment caused by insulin in the transfer of the medium's $P^{32}O^4$ to the PO_4, ATP, phosphocreatine, and hexosemonophosphate of diaphragm was about twice as great as the increment caused by insulin in the conversion of the medium's glucose to CO_2 and diaphragm glycogen. The transport of phosphate across the cell membrane by esterification is estimated to require about 2 per cent of the energy supplied by oxidative processes.

Saltzman, Abraham; Caraway, Wendell T.; and Beck, Irving A. (*Med. Serv. and Labs. of Rhode Island Hosp., Providence, R.I.*): SERUM GLUCURONIC ACID LEVELS IN DIABETES MELLITUS. Metabolism *3*:11-15, January 1954.

Fasting serum glucuronic acid and glucose levels were estimated on 37 normals, 134 diabetics on insulin, 27 diabetics who received no insulin for the preceding 24 hours, and 21 patients with liver damage. The normal corrected glucuronic acid range in the serum was 1.6 to 3.6 mg. per cent.

A significant elevation of glucuronic acid irrespective of glucose level and insulin administration was found in patients with diabetes and liver disease. It is suggested that this could be due to glycogen depletion of the liver in these states, with the elimination of metabolites by glucuronic acid conjugation.

Schwab, Louis; and Lotspeich, William D. (*Dept. of Physiol., the Coll. of Med., Univ. of Cincinnati, Cincinnati, Ohio*): RENAL TUBULAR REABSORPTION OF ACETOACETATE IN THE DOG. Am. J. Physiol. *176*:195-200, February 1954.

A study was made of the renal tubular reabsorption of acetoacetate in the dog. It was found that at normal and slightly elevated plasma levels, reabsorption of filtered acetoacetate was essentially complete, and none appeared in the urine. As the plasma acetoacetate, and thus the filtered load, increased still further, the rate of reabsorption also increased but failed to keep pace completely,

and acetoacetate excretion occurred. At filtered loads of approximately 0.8 mEq./min./m², a maximal rate of reabsorption was reached which amounted to some 0.4 mEq./min./m². At filtered loads greater than 0.8 mEq./min./m², the reabsorptive capacity for acetoacetate steadily and significantly declined until, at the highest loads studied (2.5 mEq./min./m²), it nearly ceased altogether. This declining rate of reabsorption was found to be unrelated to urine flow, to acid-base balance, or to a competitive inhibition of reabsorption between acetoacetate and beta hydroxybutyrate.

It was postulated that the causative factor in this declining rate of reabsorption is an auto-inhibition, by the acetoacetate ion itself, of some critical enzyme involved in the reabsorptive mechanism. The possibility was presented that acetoacetate "reabsorption" might represent in large part tubular "metabolism" or "utilization" of the acetoacetate ion. It was suggested that the other metabolites, which are "reabsorbed" by the tubule, be studied to determine whether their reabsorption really represents transport or whether it might represent in whole or in part tubular utilization.

Searle, G. L.; Strisower, E. H.; and Chaikoff, I. L. (*Dept. of Physiol., Univ. of California Sch. of Med., Berkeley, Calif.*): GLUCOSE POOL AND GLUCOSE SPACE IN THE NORMAL AND DIABETIC DOG. Am. J. Physiol. *176*:190-94, February 1954.

The miscible glucose pool in normal and in diabetic dogs has been determined by a method which combines a single-injection and constant-infusion technic employing minute amounts of labeled glucose. The total amount of labeled glucose administered in each experiment did not exceed 1 mg. In normal dogs weighing 6 to 8 kg., the miscible glucose pool amounts of 2 to 3 gm. In diabetic dogs, the glucose pool is increased about threefold and is restored to normal by insulin injections. It has been found in normal, diabetic, and diabetic dogs injected with insulin that the space occupied by diffusible glucose is of the order of 30 per cent of the dog's weight.

Siegal, Sheppard; and Herzstein, Joseph (*Adult Allergy and Diabetes Clins., Mount Sinai Hosp., New York, N.Y.*): ATOPY AND DIABETES MELLITUS. J. Allergy 25:25-27, January 1954.

Among 40 diabetic patients whose insulin requirements were from 50 to 110 units a day, 8 individuals were found to have either clinically manifest or latent atopy, an incidence of 20 per cent. There were 6 patients with the clinical phase of atopy and 2 with the latent phase of atopy. These observations would indicate that there exists no special relationship between the two hereditary states of atopy and diabetes mellitus. Patients with severe diabetes have not been shown to have any unusual predisposition to atopy. It appears unlikely that diabetes of the severer type is based on any immunologic mechanism such as seems to occur in rare instances of insulin resistance and allergy.

Stadie, William C. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Penn.*): CURRENT CONCEPTS OF THE ACTION OF INSULIN. Physiol. Rev. *34*:52-100, January 1954.

The author surveys in detail recent experimental data dealing with the chemical mechanisms by which insulin produces its effects upon the milieu of enzymes engaged in the metabolism of carbohydrates, proteins, and fats. Present evidence reveals no single mechanism which can explain insulin-enzyme interactions. Rather, insulin appears to act at three important loci: (1) It is concerned with the transfer of glucose across cell membranes or interfaces, (2) it influences the action of glucose-hexokinase in catalyzing the formation of a hexose-6-phosphate, the initial step in mammalian glucose metabolism, and (3) it influences the oxidative reactions concerned with the formation and regeneration of adenosine-triphosphate. Because current theory holds that protein and fat metabolism are dependent for their normal course upon unaltered glucose metabolism, disturbances in the former will result from deviations in the latter.

Sunderman, F. William (*Div. of Metabolic Res., Jefferson Med. Coll., Philadelphia, Pa.*): FURTHER MODIFICATIONS IN THE MEASUREMENT OF BLOOD GLUCOSE. Am. J. Clin. Path. *23*:193-96, February 1953.

A micro-adaptation of the Sunderman-Fuller procedure for estimating blood glucose has been described. A new tube has been designed for use with both the macro and micro procedures for estimating blood glucose and for use with either visual or photoelectric colorimetry.

Tolstoi, Edward; Given, William P.; and Douglas, Gordon R. (*2 E. 94th St., New York 28, N. Y.*): MAN-

AGEMENT OF THE PREGNANT DIABETIC. J.A.M.A. *153*: 998-1002, November 14, 1953.

The authors state that infant survival in the pregnant diabetic can be achieved without hormone therapy by use of the "clinical" method for the treatment of diabetes, with emphasis on the avoidance of ketosis. Complications, such as toxemia, hydramnios, and hypertension, in about the 30th week or shortly therafter are most serious. There is no specific treatment for them. After the 32d week, depending upon complications, premature delivery offers the best, but by no means the most certain, chance of fetal survival. The exact time for delivery cannot be determined from any specific or past experience. Cesarean section is the procedure of choice in terminating the pregnancy of the diabetic patient with complications and an excessively large infant. It is the most practical approach but does not guarantee a living child. Experienced pediatric care and treatment of the newborn as a premature infant are imperative.

Weigen, John F.; Pendergrass, Eugene P.; Ravdin, Isadore S.; and Machella, Thomas E. (*Dept. of Radiol.; Harrison Dept. of Surg. Res.; Gastrointestinal Sec. Med. Clin., Univ. of Pennsylvania, Philadelphia, Pa.*): A ROENTGEN STUDY OF THE EFFECT OF TOTAL PANCREATECTOMY ON THE STOMACH AND SMALL INTESTINE OF THE DOG. Radiology 59:92-102, 1952. (Abstracted from Surg., Gynec. & Obst. from Int. Abstr. of Surg. 96:306, March 1953.)

The study showed that hyperglycemia in the depancreatized dogs was associated with delayed gastric emptying and with prolonged small intestinal transit times. Hypoglycemia in the depancreatized dogs was associated with normal, and at times rapid, gastric emptying and small intestinal transit.

Weintraub, David H.; Calcagno, Philip L.; Kelleher, Mary K.; and Rubin, Mitchell I. (*Statler Res. Lab., Buffalo Children's Hosp. and the Dept. of Pediat., Sch. of Med., Univ. of Buffalo, Buffalo, N. Y.*): MECHANISM OF RENAL GLYCOSURIA IN ACTH-TREATED PREMATURE INFANTS. Proc. Soc. Exper. Biol. & Med. 81:542-45, November 1952.

Glycosuria resulting from ACTH administration in premature infants is due to an imbalance of glomerulotubular function demonstrated by a rise in GFR/TmG ratio. The cause of the rise in this ratio varied and was due either to a disproportionate rise in glomerular filtration rate or to a fall in glucose Tm. The nonglycosuric ACTH-treated infants did not show this rise in the GFR/TmG ratio.

Wolleager, Eric E.: LABORATORY PROCEDURES OF USE IN THE DIAGNOSIS OF PANCREATITIS. Surg. Gynec. & Obst. 96:371-74, March 1953.

By far the most important laboratory procedures for diagnosis during attacks of acute or relapsing pancreatitis are the tests for the concentration of amylase and lipase in the serum. There is a characteristic increase in the concentration of serum amylase or lipase or both. Transient increase of blood sugar and glucosuria during attacks of abdominal pain may occasionally be the first clue to the diagnosis of pancreatitis. Permanent diabetes mellitus may be expected to develop at some time in as many as a fourth of the patients with chronic relapsing pancreatitis. Diabetes is a late sign and indicates extensive destruction of the tissues of the entire pancreas. Any patient who has a long-standing history of recurring attacks of abdominal pain and in whom diabetes mellitus develops should be suspected of having chronic relapsing pancreatitis.

Zaslow, Jerry (*Albert Einstein Med. Center, Northern Div., Philadelphia, Penn.*): ACUTE PANCREATITIS ASSOCIATED WITH NECROSIS AND PERFORATION OF THE COMMON BILE DUCT. A. M. A. Arch. Surg. 67:47-51, July 1953.

Operation was carried out in two patients who had perforation of the common bile duct associated with acute pancreatitis. The indications for operation in acute pancreatitis are discussed.

Zimmerman, B. (*Dept. of Surg., Univ. of Minnesota Med. Sch., Minneapolis, Minn.*): DIABETES AND GROSS LESIONS OF THE PANCREAS. J. Clin. Endocrinol. & Metab. *14*:481-83, April 1954.

The author discusses the importance of the association between diabetes and gross lesions of the pancreas, from both a practical and historical standpoint, and feels that this association may occasionally be of great diagnostic value in a field in which more specific diagnostic procedures are unfortunately lacking.

EDITORIALS

DIABETES AND PREGNANCY

In the last few years, the relation of diabetes and pregnancy has been the subject of numerous reviews. Observations made in several countries[1-8] have supplied many thought-provoking facts. The clinical reports concentrate on such things as the management of the pregnant mother and the reduction of fetal mortality. Like the arteriosclerotic complications, the problems of the pregnant diabetic have grown rapidly since the discovery of insulin and the prolonged survival of young women with diabetes. The physiological implications of many of the observations of the last ten to fifteen years are assuming more and more importance. Some of the facts may be put together as follows.

Diabetic women of childbearing age may have children at practically no increase in risk to themselves, provided their diabetes receives good care. There is still a considerably increased fetal wastage. All authorities agree that good management of the diabetes, which probably means good nutrition,[9] must be the physician's first concern. The hormonal response to pregnancy includes a great excess in the production of adrenal cortical hormones,[10] this excess approaching the quantities excreted in Cushing's syndrome (Touchstone, unpublished). However, the adrenal hormones thus measured in blood and urine are essentially the same during pregnancy in diabetic and normal women. Since normal women have no disturbance of carbohydrate metabolism from these endocrine responses to pregnancy, one assumes that the increased insulin requirement of pregnant diabetics, which commonly amounts to a total of 90 units daily in the third trimester, is the result of an increased demand coupled with their deficiency of insulin. The deficiency of the insulin reserve of the "prediabetic" woman during pregnancy may also be revealed by sugar tolerance tests performed after the fourth month.[4] The prevention of large babies by modern pelvimetry and cesarean section when indicated improves the outlook for mother and child. The older, and well-confirmed, studies on the increased frequency of large babies (with birth weight over 10 lb. or 4500 gm.) in women destined to become diabetic 5 to 15 years later[8] offers a possible opportunity to anticipate the onset of frank diabetes by many years. All authors agree on this increased frequency of large babies in "prediabetics" and an extensive investigation of pregnant women is being undertaken by Dr. Hugh L. C. Wilkerson and his associates of the U. S. Public Health Service in cooperation with the Children's Bureau of the Massachusetts Department of Public Health to see if a new avenue of preventive medicine can be opened.

The experimental and clinical hypotheses of Hoet[4] and others[1-3,5-7] are still young and much work remains to be done before pregnancy can be viewed in true perspective as a factor predisposing to diabetes in those who already have some form of familial (genetic or developmental) defect. In this difficult area there are many discrepancies and inconsistencies which are not labored here because their resolution demands more investigation rather than editorial ink. In the last analysis, students of diabetes will be grateful to all of the observers who have advanced this approach to the study of a disease whose natural history seems to extend from the patient's grandparents to the patient's grandchildren.

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POSTGRADUATE COURSES

The major objective of the American Diabetes Association is to bring about a clearer understanding of diabetes so that patients may experience a minimum of difficulty and discomfort. Continuing investigations in the various research centers are yielding important new information bearing on the cause, pathological physiology, clinical manifestations, complications, new methods of therapy, and prevention of diabetes. The health of the future diabetic depends on the researches of today. A large amount of important knowledge has been gained in the last quarter century. Much of this has not yet found its way into the daily routine practice of physicians who represent the shock troops in the battle for better diabetes control.

While research is being encouraged and supported at various centers, it is important that the deliberations of authorities in the basic sciences and at the clinical level be given adequate presentation and interpretation. It is self-evident that the better the understanding on the part of the physician and the more intelligent and cooperative his patient, the more satisfactory will be the results. Education then, follows research as an important principle for diabetes control.

The American Diabetes Association is an organization made up of basic scientists and clinicians whose interests include research, the care of patients, and education of the profession and public at large.

The policies of the Association deal with encouragement of research and an expansion of training programs. Through its Journal DIABETES the various areas of research in nutrition, metabolism, endocrine disorders and associated fields are given scope for expression. The Journal is filling an important need of medical science, as is demonstrated by the increase in its circulation. Many of its papers are derived from the annual spring meeting of the Association which furnishes an opportunity for investigators to present their findings to the membership of the Association.

A few years ago the Council of the Association appointed a committee on Postgraduate Courses. Two courses have already been given with gratifying success —the first at Toronto in January 1953 and the second at the Mayo Clinic in Rochester, Minnesota, in January 1954. The third Postgraduate Course will be given January 19-21, 1955, at The Lankenau Hospital in Philadelphia. The first two courses were oversubscribed and unfortunately not all those desiring to enroll could be accommodated. It is the policy of the Association to give preference to those applicants who were not accepted for the preceding courses and who desire to enroll in the next following course.

While the courses were in progress, members of the class were requested to give their frank comments regarding topics, speakers, the scope of the course and any other pertinent information they desired to offer. This has resulted in a considerable number of exceedingly helpful comments. Some of them refer to omissions in subject matter. For example, requests have been made several times for a discussion of "The Elderly Diabetic"; others requested a discussion on "The Treatment of Dia-

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The report from Dr. H. S. Everett of St. Stephen, New Brunswick, Canada, contained both praise and constructive criticism. Ed.

A general practitioner looks back on the Second Annual Postgraduate Course. What a stimulating experience and what a privilege to meet and listen to the great and near-great in the diabetic world. Excellent papers, ably presented, good fellowship and hospitality from all I met. The general high plane of the whole meeting made it a very memorable experience and one I hope to repeat at Philadelphia next year.

I was somewhat perturbed, however, by the attitude of some of the speakers towards the use of insulin, namely, that one must be very careful and that severe or even mild reactions are very much to be dreaded, much more so than brick tests of the urine. Also that absolute control of diabetes was a goal that could only be attained in a few special cases and in fact wasn't even a goal. . . . I must confess that for the last twenty years, during which time I have successfully treated many diabetics, I have made absolute control the goal for all. . . . Naturally, I have tried to avoid severe reactions but I have never worried about them when they did occur nor have I seen any harm come from them and I have seen some very severe reactions in labile diabetics. . . .

I throw a challenge to the specialists in diabetic care and treatment. Are you giving us general practitioners and the millions of diabetics on this continent and in the world the proper lead in this most important question?

betes in Association with Other Diseases." Some applicants requested a four-day rather than a three-day course. There was also the usual and important comment that speakers should not use slides containing a large mass of fine print that the audience could in no way encompass. The Committee was impressed with the suggestions concerning intermediary metabolism, nutrition and dietetics, a larger consideration of the liver and the blood in association with diabetes, and request for a discussion on normal metabolism of carbohydrates, proteins, and fats. A number of those attending the course requested that printed summaries of each presentation be furnished before the course was given. This entails a great amount of detail in preparation and often is difficult to accomplish.

From a report submitted by a general practitioner in St. Stephen, in New Brunswick, the Committee was much impressed by the awareness of the practicing physician of the need for a higher standard of treatment for diabetes and the desire to learn how to maintain the best possible control. (See footnote page 250.)

For the Third Postgraduate Course which will be held in Philadelphia next January, the Committee has conferred with a number of authorities of the various medical faculties in Philadelphia. It has also requested suggestions from members of the Council of the Association and has carefully reviewed the comments of those in attendance at the two previous courses. From this information the Committee will endeavor to organize a course which will be offered next January that will emphasize normal nutrition, the pathological physiology of diabetes, the diabetic child, the elderly diabetic, new data on the origin of complications, new approaches to diet planning, and certain other highlights bearing on diabetes. The Committee hopes to offer three clinics with presentation of patients.

It has been recognized that the presentation of new data in each course is essential rather than a review of material and information which already is the common knowledge of the alert modern physician.

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THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST

Amatuzio and his associates[1] have developed a rapid and practical modification of the intravenous glucose tolerance test.[2] Twenty five grams of glucose, as a 30 per cent solution in distilled water, are administered intravenously in four minutes. Blood samples are obtained for sugar determinations immediately before, immediately after completion of the glucose infusion, and thereafter every 8 minutes for 64 minutes. A capillary blood sugar method is used. The loss of glucose in the urine is relatively insignificant during the one-hour period of the test and even in diabetics does not exceed 10 per cent of the amount administered. When the logarithm of the amount of glucose in excess of the fasting blood glucose ("glucose excess") is plotted on semilog graph paper against the time in minutes, a straight line relationship is obtained, from which the disappearance rate of glucose from the blood may be obtained either by graphic means or by calculation. A highly significant difference between normal individuals, mild diabetics, and severe diabetics could be established for the rate of glucose disappearance, expressed as per cent per minute. With diabetes, glucose disappearance rates were uniformly lower than normal. As might be expected, various conditions including obesity, inflammatory disease, uremia, carbohydrate starvation and decompensated portal cirrhosis also revealed a decreased rate of glucose disappearance. The rate of fall of the "excess glucose" depends upon both peripheral utilization of glucose and its storage in the form of liver glycogen. Like other tests the one described in no way differentiates disturbances in storage from those of utilization.

The advantage of this test over oral tests (shared with other intravenous tests) is that changes in gastrointestinal motility and rate of absorption do not influence the results. This test has definite advantages over other types of intravenous testing, such as that developed by Thorn and his associates,[3] in that it is less time consuming and the results are relatively independent of the dosage of glucose administered for doses of 25 gm. or more. Another advantage of this test is that any blood sugar method may be used, even those that do not determine true blood glucose. The authors have shown that nonfermentable reducing substances remain constant during the test. Since the error in blood glucose determination is constant and the results are expressed as differences in blood sugar levels, the conclusions of the test are independent of the method used for determination of blood sugar. The test appears to have an excellent reproducibility in the same individual at different times.

The linear nature of the curve indicates that the process of removal of glucose from the blood is governed by the laws of unimolecular reactions, where the rate of reaction varies with the concentration of the reactant. Such conditions would be met if all the mechanisms for removal of glucose from the blood involved diffusion into the intracellular environment,

namely, liver and peripheral tissues. It is of interest that the action of insulin is thought to be exerted upon such a process of diffusion.[4]

With this excellent method three physiological processes have been investigated in man by Amatuzio and his associates.[5] As might be expected,[6] 4 units of insulin given with the glucose intravenously were shown to increase the rate of disappearance of glucose from the blood by 110 per cent. In contrast, 0.5 mg. of epinephrine given subcutaneously thirty minutes prior to carrying out the test, led to a 66 per cent decrease in the disappearance rate of glucose. This decrease may be ascribed to increased glycogenolysis[7] and/or peripheral inhibition of glucose utilization.[8] While a rise in blood sugar levels following such a dose of epinephrine within 25 minutes and lasting up to 90 minutes had been demonstrated in man[9] the effect upon the removal of added glucose from the blood had not been previously studied.

The glucose disappearance rate was investigated in 17 patients with moderate to severe hyperthyroidism and was found to be completely unrelated to the severity of the disease. In 15, the rate was high or normal. In 2, it was slow. This is not surprising because of the pathophysiology involved. Peripheral utilization of glucose is increased[10] by the general acceleration of metabolism. Yet glucose storage in the liver is impaired due to a cirrhotic process[11] and impairment of beta-cell function from exhaustion is accompanied by a decrease in endogenous insulin production.[12] Thus glucose utilization is decreased. These facts might also explain why after treatment with radioactive iodine, an establishment of euthyroidism in the 15 patients with normal or fast rates of glucose disappearance, this became slower in 8, remained unchanged in 5, and rose slightly in 2, while in the 2 originally showing slower than normal rates of glucose disappearance it became faster in 1 and slower in the other.

The rapid intravenous glucose tolerance test as developed by Amatuzio and his colleagues lends itself admirably to further clinical investigation because of its relative simplicity, rapidity, and reproducibility.

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BOOK REVIEWS

NUTRITION AND PHYSICAL FITNESS: *By L. Jean Bogert, Ph.D., Formerly Instructor in the Department of Medicine, University of Chicago; Instructor in Experimental Medicine, Yale Medical School, and Lecturer in Chemistry, Connecticut Training-School for Nurses, New Haven; Professor of Food Economics and Nutrition, Kansas State Agricultural College, Manhattan; Research Chemist, Obstetrical Department, Henry Ford Hospital, Detroit. $4.50, pp. 664, illustrated. W. B. Saunders Company, Philadelphia, Pa., 1954.*

The appearance of the sixth edition of this important work on *Nutrition and Physical Fitness* by a recognized

authority in the field of nutrition, L. Jean Bogert from Berkeley, California, is a happy event. Those who have read and used the earlier editions will find in this latest text a large amount of new material. In the preface the author indicates that more than 60 per cent of this volume is entirely new and the remainder has been completely revised. In no field of medical science in the past decade has there been greater activity of importance than in the field of nutrition and metabolism.

The book is divided into four parts dealing with Body Needs, Body Processes, Meal Planning, and Diet for Special Conditions. At the end of each chapter there is a section on questions and problems which should be exceedingly helpful to teachers of nutrition. The list of supplementary reading suggested at the end of the chapters, while not inclusive, nevertheless contains many of the more important references pertinent to the material discussed in the chapter. The chapter on carbohydrates, fats, and proteins contains the standard information. The chapter on basal metabolism and temperature regulation is exceedingly well done. The discussion on protein requirements and protein balance fails to mention the work of Kountz and others on the protein requirements of individuals in the higher years.

It is unfortunate that the important topic of Diet After Forty did not receive the critical attention that this rapidly expanding area merits. The relationship between continued vitality and vigor in the mature and higher years of life and nutrition is being studied by a number of investigators. The relationship between nutrition, particularly total intake, fat content of the diet, and vascular degeneration merits careful evaluation in any book on nutrition.

The chapter on Overweight accepts the traditional interpretation of weight control. There is a passing reference to the experiments of Jean Mayer, but no mention is made of the pioneer work of John Brobeck and his associates, who were among the first to identify areas in the hypothalamus as centers for the control of body weight and appetite.

At the end of the book there are the usual appendices with reference to the nutritive value of foods in average servings. There are also the usual tables of Weight-Height-Age approximations of normal.

The author has added to her stature as an authority in the field of nutrition by the appearance of this useful volume. The publishers are to be congratulated on the attractive format and the clearness of printing. The illustrations, an increase to 111 over the preceding 96, might have been reproduced with greater clarity.

This book is recommended to teachers of nutrition and students who hope for better understanding of basic facts concerning the nutritional needs of the human body.

The Search For Hidden Diabetes

The protean specter of diabetes mellitus haunts the consulting room of every practicing physician. It lurks behind the folliculitis, furunculosis, and pruritus ani in the office of the dermatologist. It peers out from retinal microaneurysms, pigmentation, hemorrhages, and retinitis proliferans at the ophthalmologist. It hides behind altered sensation and reflexes in the clinic of the neurologist, and leers through an albuminous cloud in the test tube of the urologist. It troubles the sleep of the surgeon concerned about ketosis and wound healing; and of the obstetrician vacillating between forceps and cesarean. It hides behind the cough of the phthisical, and the elevated T-wave on the cardiogram. It complicates the peaceful diagnostic life of practitioner and specialist alike.

It is the responsibility of medical men to be wary of this dissimulator; it is also the responsibility of the profession to discover diabetes as early as possible and to institute proper management. Poor control of diabetes usually results in a high incidence of complications: infection, acidosis, retinitis, nephropathy, vascular calcifications, and neuropathy. Good control reduces the incidence of these complications and increases longevity in the diabetic.

For the early detection of diabetes, each physician-practitioner and specialist alike—must perform a screening test, even though it be only a urine test for glucose one hour after a high carbohydrate meal, on every patient he sees.

Each of us owes it to the community to cooperate with the intensive campaign of diabetes detection and education; but let us not forget that this is a year-round program.

Milton R. Weed, M.D., in the *Detroit Medical News*, Nov. 16, 1953.

Joseph H. Barach

Cecil Striker, M.D., Cincinnati

Dr. Joseph H. Barach of Pittsburgh was one of the group of physicians headed by Dr. Cecil Striker who worked together to found the American Diabetes Association. He served as a member of the Council from the beginning of the organization and he became the fourth president of the Association. A review of his career is presented to the readers of DIABETES by his friend and coworker in the Association, Dr. Striker.

Dr. Joseph H. Barach has passed away. He died on March 7, five days before his seventy-first birthday. To those of us who knew him intimately, his passing came as a great shock and his loss will be keenly felt. For those of us who knew him less intimately, it is well here to recognize his personality and his contribution to science in general and to the American Diabetes Association in particular.

Dr. Barach attended the University of Pittsburgh and received the degree of Doctor of Medicine in 1903. Later he was a graduate student of Columbia University and a resident pathologist and intern at the Western Pennsylvania Hospital. He became an Associate Professor of Medicine at the University of Pittsburgh School of Medicine and also Medical Director of the University Clinics in 1930. He served as Captain in the Army Medical Corps in the first World War. Dr. Barach's name was inscribed on the Wall of Fame of the American Common at the World's Fair of 1940 in New York for "having made notable contribution to our living, ever-growing democracy devoted to peace and freedom."

Dr. Barach was both austere and affable. Once the barrier of austerity was penetrated his sterling qualities glittered and his devotion to his friends unfolded. He possessed the rare combination of fidelity to work and capacity to play. He had many attributes, but above all towered the single underlying one of self-discipline. Other men might have elected to relinquish responsibilities, but even during his last illness Dr. Barach was intimately involved in broad scientific responsibilities. He was methodical in thought and activity. His every

day was outlined and programmed. Where others would trust to fate, he had a design for living. His schedule of activities was always full, and if one discussed this with him, his great lament was that there was not time to do more.

This pattern of living was reflected in Dr. Barach's mode of thought. Each scientific undertaking and each accepted responsibility was planned well in advance and in an orderly fashion. His charts, his files, and his scientific contributions indicate a polished effort culminating in a fine product.

Counterbalancing Dr. Barach's fidelity to work was his capacity to play. Many of us will most happily recall our visits to his "other" home—Mountain Hill Farm, Manteo, N. C. Here he gathered many of his medical friends for conference and play. Here it was that he was almost at his best. He displayed his fishing tackle, his guns, his boats and above all his ability to use them. Here was the real host unstinting in his efforts to make one's visit a highlight. Here it was that he indulged in exaggerations in talking about his fishing and shooting. He was an excellent sportsman but exercised the right of every sportsman to magnify his prowess. In the past several years he spent time during all seasons of the year at Manteo and became an integrated citizen of the community. On his farm in addition to his sports activity, he seriously undertook the development of the raising of figs and had acquired considerable success in this project.

Being a great self-disciplinarian, Dr. Barach was able to make many important contributions to the medical literature. He published one hundred and fifty scientific articles, and contributed to the *Cyclopaedia of Medicine,* and to Stroud's *Diagnosis and Treatment of Cardiovascular Disease* and was himself the author of three books. One, entitled *Self Help for the Diabetic,* from the University of Pittsburgh Press, has gone into its sixth printing. In 1950 Dr. Barach contributed from the Oxford University Press *Diabetes and Its Treatment* and *Food and Facts for the Diabetic.* He was one of the earliest contributors to the literature on the use of insulin; in fact, he was believed to be the first American author of a paper on insulin. Early in his career he did sound work in hydrotherapy and collaborated with Dr. Simon Baruch in this project.

Dr. Barach's early efforts were devoted to cardiovascular diseases, but shortly after the discovery of insulin his attention was focused on diabetes, and thereafter he published many papers on the clinical and experimental phases of his subject. At the time of his death, he was intimately involved in a long-term project at the University of Pittsburgh, studying the relationship of atherosclerosis to diabetes.

Dr. Barach's particular devotion was to the American Diabetes Association. When the history of this association is written, it will be clearly seen that much of its amazing success is the result of Barach's ceaseless devotion. In the early days of the development of the Association, it was he who drew up many of the plans for its development, and it was he who executed many of these plans. A long chapter in the history of the Association could be devoted to his activities. He sparked every Council meeting and had the enviable capacity to accomplish much and to overcome the hurdles in the early history of the organization.

Dr. Barach frequently recalled that one of the highlights of his medical life was the meeting of the American Diabetes Association in Toronto on the twenty-fifth anniversary of the discovery of insulin. He was the president of the Association at this time and devoted much time and energy to the success of this remarkable meeting. He labored to bring together world authorities on diabetes to pay tribute to the discoverers of insulin, and for the record it is worthy of note that at that unprecedented meeting were Drs. Joslin, Best, Wilder, Lawrence, Hagedorn, Houssay, and Opie.

Dr. Barach was the fourth president of the American Diabetes Association, serving during World War II from 1944 to 1946; he was treasurer from 1948 to 1952. From the Association's inception in 1940 he was an active member of its Council. He was awarded the Banting Medal of the American Diabetes Association in 1946.

Dr. Barach was a member of many other scientific organizations, among them the American College of Physicians, of which he was a Fellow, the American Association for Advancement of Science, and Sigma Chi. He was chairman of the Metabolism and Endocrinology Section, Research Grants Division, United States Public Health Service, from 1946 to 1951. He had also been a member of the National Advisory Arthritis and Metabolic Diseases Council, National Institutes of Health, Public Health Service, since 1952. Thus one can see that he had a guiding hand in many scientific endeavors.

He is survived by a devoted wife, who spurred him on and encouraged him in his medical activities, and two sons, Joseph L. Barach, a physicist, and Richard L. Barach, M.D.

The American Diabetes Association was a part of the life of Joe Barach. Its growth and its perpetuation are secure because of him. His name will always be prominent in the annals of the Association.

Organization Section

Third Postgraduate Course January 19-21, 1955

The Council of the American Diabetes Association has approved plans for holding the Third Postgraduate Course in Philadelphia, Pa., Jan. 19, 20 and 21, 1955. The Course will be under the auspices of the Committee on Professional Education chaired by Edward L. Bortz, M. D., who will also serve as Director of the Course.

The meeting will be devoted to diabetes and basic metabolic problems. The following general subjects are scheduled for a half-day each: Normal Metabolism, The Pathological Physiology of Diabetes, The Young Diabetic, Obesity, The Status of Complications.

The sessions will be held at the new Lankenau Hospital and the Bellevue-Stratford Hotel will serve as Association headquarters. A dinner and social hour will be held Thursday evening, January 20.

The registration fee for the three-day course is: $40 for members, $75 for nonmembers. Applications for registration should be sent to J. Richard Connelly, Executive Director, at the National Office.

The Program will be published in DIABETES and Preliminary Programs will be sent directly to all the members.

National Office Moves

As the membership was informed by mail the latter part of April, the American Diabetes Association moved April 28 to new offices at 1 East 45th Street, New York 17, New York.

The new location is in midtown Manhattan and only a few blocks from the previous address. The move, nearly doubling the previous office space, was necessary to maintain the program and services rendered by the Association.

All members and readers of the Journal are asked to be sure to note the change of address. Everyone is cordially invited to drop by to see the new offices.

Research Funds Available From The American Diabetes Association

As previously announced in DIABETES, two fellowships of approximately $2,500 each are available for adequately trained investigators who will give their full time to a problem in the general field of diabetes in the laboratory or clinic of a recognized authority on this subject. Applications should be sent to the Executive Director at the National Office.

New Members

The following Active Members were elected as of May 1 and June 1, 1954:

Alabama	
McMahon, John M.	Bessemer
California	
Caffee, James L.	Fresno
Donald, Russell A.	Fresno
Fulmer, Harlan F.	Fresno
Kanne, William P.	Fresno
Mieras, Marion D.	Whittier
Sorsky, Eliot	Fresno
Thorburn, Jack D.	Fresno
Tillotson, Irving G.	Fresno
Vaughan, Robert A.	Fresno
Colorado	
Badger, E. Bruce	Denver
Clark, Paul M.	Denver
Clarke, James P.	Denver
Donovan, Edward J.	Denver
Frangos, Peter G.	Denver
District of Columbia	
Smith, Robert L.	Washington
Florida	
White, Lavere G.	Ft. Lauderdale
Georgia	
Bloom, Walter Lyon	Atlanta
Jones, Eugenia C.	Atlanta
Idaho	
Forney, William D.	Boise
Illinois	
Conley, Henry H.	Park Ridge
Foa, Piero P.	Chicago
Young, Warren W.	Chicago
Indiana	
Alfaro, Raul D.	Indianapolis
Young, Woodson C.	Indianapolis
Iowa	
Bailey, Robert O.	Waterloo

Michigan	
Maire, Edward D.	Detroit
Parnell, John W.	Detroit
Minnesota	
Berman, Reuben	Minneapolis
Cohen, Ephraim B.	Minneapolis
Freedman, Marshall A.	Rochester
Neff, Walter S.	Virginia
Rogers, Arnold G.	Rochester
Smith, Roger C.	Rochester
New Jersey	
Mufson, Monroe H.	Denville
New York	
Blum, Robert	Buffalo
Burtch, Robert B.	Alexandria Bay
Greenwald, Jerome J.	Brooklyn
Korsch, Barbara M.	New York
McGan, Harold P.	Albany
Painton, J. Frederick	Buffalo
North Carolina	
Lister, Leonard M.	Durham
North Dakota	
Barnard, Donald M.	Fargo
Ohio	
Ayres, Roland W.	Van Wert
Morrice, George, Jr.	Columbus
Owens, J. Evan	Cleveland
Vincent, Donald J.	Columbus
Wilson, Charles W.	Marion
Oklahoma	
O'Meilia, William J.	Tulsa
Pennsylvania	
Coleman, Thomas H.	Carbondale
Farber, Harold I.	Reading
McNeill, John R.	Erie
Pearlman, William	Wilkes-Barre
Smith, Francis A.	Pittsburgh
Viener, Bernard	Harrisburg
Viglione, Michele	Philadelphia
Tennessee	
Nelson, William A.	Knoxville
Texas	
Pohl, Donald E.	Austin
Utah	
Bennion, William H.	Salt Lake City
Virginia	
Hortenstine, John C.	Winchester
Washington	
Berghan, Robert	Spokane
West Virginia	
Lindsay, John D., Jr.	Fairmont
Wyoming	
Leeper, Ben Morris	Cheyenne

OTHER COUNTRIES

Canada	
McNabb, Alan R.	Hamilton, Ont.
Tisdale, Paul K.	Winnipeg, Man.
Greece	
Woylas, Basil G.	Athens
Italy	
Polosa, Pietro	Sicily

News of Affiliate Associations

The CONNECTICUT DIABETES ASSOCIATION held its annual meeting at the Buckley High School in Hartford April 29. The session was scheduled in conjunction with the annual meeting of the Connecticut State Medical Society. C. N. H. Long, M.D., of Yale University, was the principal speaker.

The LOS ANGELES DIABETES ASSOCIATION convened for its yearly meeting April 24 at the Good Samaritan Hospital at Los Angeles. Peter H. Forsham, M.D., Associate Professor of Medicine at the University of California School of Medicine, San Francisco, spoke on "What's New in Endocrinology."

The NEW JERSEY DIABETES ASSOCIATION met for its Third Clinical Society Meeting of this organizational year at the Essex House in Newark April 28. The session consisted of an informal presentation and discussion of a selected number of case studies.

The Section on Metabolism, Medical Society of New Jersey, held a meeting at Haddon Hall Hotel, Atlantic City, New Jersey, on May 17. The following program was presented: "Nephritis in Diabetes," by E. O. Bauman, M.D., with Selma Weiss, M.D., Louis Grunt, M.D., and Otto Brandman, M.D., as collaborators and discussors; "Arteriosclerosis as a Metabolic Disease," a panel discussion by Stewart Alexander, M.D., Albert G. Markel, M.D., and James F. Gleason, M.D., with G. M. Knowles, M.D., as moderator; "Radioactive Iodine in the Diagnosis and Treatment of Thyroid Disease," by J. E. Ralls, M.D., of the Sloan-Kettering Institute and Cornell Medical School.

The TEXAS DIABETES ASSOCIATION met in San Antonio May 2. Herbert Pollack, M.D., of New York City, was the guest lecturer at the annual gathering and presented two papers entitled "The Management of Diabetic Coma" and "Dietary Requirements for the Diabetic Patient." In addition, Dr. Pollack participated in a panel, "The Newly Discovered Diabetic," with the following other members of the American Diabetes Association: Merton Minter, M.D., Hugo Engelhardt, M.D., Edwin L. Rippy, M.D., and Raymond Gregory, M.D. Also included on the program were these papers: "The Relationship of Diabetes to Heart Disease" and "Posthypoglycemic Encephalopathy" by James Skelton, M.D., and George M. Jones, M.D., respectively.

The VIRGINIA DIABETES ASSOCIATION cooperated in preparation of the program for the Fourth Annual Scientific Assembly of the Virginia Academy of General Practice held at the Jefferson Hotel, Richmond, Va., May 5-7, 1954. Members of the American Diabetes Association who took part include: James M. Moss, M.D., Alexandria, Va., "The ADA Food Exchange Tables," and Thomas S. Edwards, M.D., Charlottesville, Va., "Considerations of Insulin Problems in Severe Diabetics (with discussion of a new type of insulin)." William R. Jordan, M.D., Richmond, Va., moderated a panel discussion of "Diabetes for the General Practitioner," with Henry B. Mulholland, M.D., Charlottesville, Va., as a panelist. Edward J. Stieglitz, M.D., Washington, D.C., discussed "Anticipatory Medicine in Later Maturity."

News Notes

Second Congress of the International Diabetes Association

The Second Congress of the International Diabetes Federation will be held in Cambridge, England, July 4-8, 1955. Sir Lionel Whitby, K.V.O., M.C., Master of Downing College, Cambridge, will be Honorary President. The Diabetic Association (Great Britain), 152 Harley Street, London, W.1, will act as host. Further information may be secured from Mr. James G. L. Jackson, of that Association, or from Dr. F. Gerritzen, Secretary-Treasurer, International Diabetes Federation, 33 Prinsegracht, The Hague, Netherlands.

American College of Physicians Meeting

The American College of Physicians held its Thirty-Fifth Annual Session April 5-9 at the Conrad Hilton Hotel in Chicago. Two members of the American Diabetes Association are Regents of the College: Edward L. Bortz, M.D., Philadelphia, Pa., and Dwight L. Wilbur, M.D., San Francisco, Calif. Members who served on committees for that meeting include: Jerome T. Paul, M.D., Committee on Auditorium; Arthur R. Colwell, Sr., M.D., Henry T. Ricketts, M.D., and Willard O. Thompson, M.D., Committee on Panel Discussions; Thomas J. Coogan, M.D., Committee on Televised Clinics.

Edward L. Bortz, M.D., served as presiding officer for the April 8 morning lecture. Salvador Zubiran, M.D., Mexico, D. F., discussed "The Endocrine Disturbances and Their Dietetic Background in the Undernourished of Mexico." Panel discussions and clinical-pathological conferences in which members of the Association took part include: "Diabetes," Moderator Henry T. Ricketts, M.D., Arthur R. Colwell, Sr., M.D., Jerome W. Conn, M.D., Randall G. Sprague, M.D. Henry T. Ricketts, M.D., participated in a panel discussion of pancreatic disease Wednesday, April 7, and Edward L. Bortz, M.D., was moderator at a clinical-pathological conference the same afternoon.

Henry T. Ricketts, M.D., presented "Problems in the Treatment of Diabetes" at a Hospital Clinic held at Albert Merritt Billings Hospital Thursday, April 8. Arthur R. Colwell, Sr., M.D., presented "Selective Treatment of Diabetes Mellitus," and Randall G. Sprague, M.D., presented "Hyperfunctioning Lesions of the Adrenal Cortex," at Passavant Memorial Hospital. Randall G. Sprague, M.D., participated in a clinical-pathological conference Friday afternoon, April 9.

Scientific Meeting of the American Heart Association

The American Heart Association held its Scientific Meeting April 3-4, 1954, at the Conrad Hilton Hotel, Chicago, Ill. Members of the American Diabetes Association who took part include Manuel Gardberg, M.D., New Orleans, La., "The Significance of the Effects of Dipole Eccentricity in Electrocardiographic and Vectorcardiographic Analysis"; Lawrence Greenman, M.D., and T. S. Danowski, M.D., (with F. A. Weigand, M.D.), "Cortisone, Dietary Electrolytes and Penicillin in Treatment of Initial Attacks of Rheumatic Carditis"; Irving M. Liebow, M.D., and Max Miller, M.D., (with Herman K. Hellerstein, M.D.), "Arteriosclerotic Heart Disease in Diabetes Mellitus"; Joseph Weinstein, M.D., (with

Isidore Stein, M.D., Seymour H. Rinzler, M.D., and Janet Travell, M.D.), "The Ergonovine Test in the Diagnosis of Coronary Insufficiency."

37th Annual Meeting of the American Dietetic Association

The American Dietetic Association will hold its 37th Annual Meeting in Philadelphia, Pa., October 26-29. Among members of the American Diabetes Association who will participate are Waldo E. Nelson, M.D., of Philadelphia, who will discuss control of diabetes in children. Henry T. Ricketts, M.D., of Chicago, will participate in the diet therapy sessions and Herbert Pollack, M.D., of New York City, will present a paper entitled "Adequate Therapeutic Diets."

Award of the First Russell M. Wilder Fellowship

The National Vitamin Foundation announced that Willard Arthur Krehl, Associate Professor of Nutrition at Yale University School of Medicine, was awarded the first Russell M. Wilder Fellowship. The $15,000 three-year Fellowship was established to encourage outstanding persons holding doctorate degrees to further their education in nutrition and related subjects and to continue to expand their research and educational activities in nutrition.

Copies of Dr. Allen's Book on *Glycosuria and Diabetes* Still Available

As announced in the March-April issue of DIABETES, copies of *Studies Concerning Glycosuria and Diabetes,* by Frederick M. Allen, M.D., published by the Harvard University Press in 1913, are still available. They may be obtained without charge through the courtesy of a $1,000 grant from Eli Lilly and Company.

The book describes the production of diabetes by partial pancreatectomy, the first experimental production of hydropic degeneration of pancreatic islands and other early experimentations.

In view of the importance of the book for historic and reference purposes, preference will be given first to libraries and then to interested individuals. Requests for the book should be sent to Mr. J. Richard Connelly, Executive Director, at the National Office.

Personal

Louis K. Alpert, M.D., of Washington, D. C., on July 1 will assume duties as Clinical Professor of Medicine at The George Washington University School of Medicine. Among his other duties Dr. Alpert will be responsible for the clinical direction of a new cancer research program. At present Chief of Medical Service at Mount Alto Veterans Hospital, Dr. Alpert will continue to serve as consultant.

Morton Berk, M.D., of Honolulu, reported a series of cases on the effect of digitalis on the electrocardiograph at a meeting of the members of the American College of Physicians on February 18 in Honolulu.

T. S. Danowski, M.D., of Pittsburgh, has received a grant of $3,850 from the American Urological Research Foundation for studies of the renotropic property of growth hormone in chronic renal disease.

Frank Gregg, M.D., of Pittsburgh, Pa., will be Co-director of the Postgraduate Course of the American College of Physicians entitled "Selected Subjects in Internal Medicine," to be held October 25-30 in Pittsburgh.

John Eager Howard, M.D., of Baltimore, Md., presented the Guiteras Lecture at the Forty-ninth Annual Meeting of the American Urological Association which was held in New York City May 31-June 1-3, 1954.

Laurance W. Kinsell, M.D., of Oakland, Calif., is co-author with Bruce M. Anderson, M.D., of Oakland, Calif., of a paper entitled "Anesthesia Management During Hypophysectomy for Fulminant 'Juvenile' Diabetes" to be presented October 25 at the annual meeting of The American Society of Anesthesiologists to be held in Cincinnati, Ohio.

Arnold Lazarow, M.D., of Cleveland, Ohio, spoke May 26 on the "Methodology and Instrumentation in Microanalysis" at a Symposium on the Recent Developments in Instrument Techniques and Applications held at the National Institutes of Health at Bethesda, Md. The Symposium was sponsored by The Washington Sections of the American Chemical Society, Instrument Society of America, and the American Association of Clinical Chemists.

Alexander Marble, M.D., of Boston, addressed the Lay Society of the New York Diabetes Association on May 25. In his talk, "The Transition Period of a Child

Diabetic to a Young Adult," he emphasized the role of camps for diabetic children in helping them make satisfactory adjustment to their ailment.

Edwin L. Rippy, M.D., as President of the Dallas (Texas) School Board, appointed a four-member committee to investigate the feasibility of building an educational television station in Dallas.

Edward J. Stieglitz, M.D., of Washington, D. C., presented a paper, "Constructive Health-Management's Stake in Industrial Health Programs," at the 1954 Industrial Health Conference at Chicago, April 26-30.

Obituaries

William H. Gillentine, M.D., of New Orleans, a member of the American Diabetes Association since 1941, died April 16 at the age of 45.

A graduate of Tulane University of Louisiana School of Medicine, Dr. Gillentine had been a member of its Faculty since 1933. He was a Fellow of the American College of Physicians and was certified by the American Board of Internal Medicine in 1941.

Among his local medical activities, Dr. Gillentine served as Treasurer and President of the New Orleans Graduate Medical Assembly and was affiliated with Charity Hospital of Louisiana, Southern Baptist Hospital, Touro Infirmary and Ear, Eye, Nose & Throat Hospital of New Orleans, as well as the Hutchinson Memorial Medical Clinic of Tulane University.

Samuel Gitlow, M.D., of the Bronx, New York, died early in the year in Miami, Florida. An Active Member of the American Diabetes Association since 1941, Dr. Gitlow was 64 years old. A graduate of Columbia University College of Physicians and Surgeons in 1912, Dr. Gitlow interned at Lebanon Hospital. He was a Fellow of the College of American Pathologists and a member of the New York Academy of Medicine. He served as president of the Bronx County Medical Society in 1928, and was also president of the North Bronx Medical Society in 1943, and of the Bronx Pathological Society in 1933.

Dr. Gitlow was assistant professor of biological chemistry at the College of Physicians and Surgeons in 1917-18. Associated throughout his career with Lebanon and Daughters of Jacob Hospitals, he served variously as chief of the medical and diabetic clinics, pathologist, attending physician, and consultant. He had been retired for several years.

Willard Owen Thompson, M.D., of Chicago, an Active Member of the American Diabetes Association, died on March 23. He is survived by his widow, Phoebe K. Thompson, and four children.

Dr. Thompson was born Feb. 17, 1899, in Fredericton, New Brunswick, Canada, the son of Samuel Sterling and Mary Owen Thompson. He received his B.A. degree from Dalhousie University, Halifax, Nova Scotia, in 1919, and his M.D. degree from Harvard Medical School, Boston, in 1923. He interned at the Boston City Hospital and from 1925 through 1929 was a graduate assistant and research fellow in medicine at Harvard Medical School and at the Massachusetts General Hospital, where he was in charge of the Metabolism Laboratory.

Dr. Thompson went to Chicago in December 1929, where he was a member of the faculty of Rush Medical College from 1929-41, and of the University of Illinois College of Medicine from 1941 until the time of his death. He then held the position of Clinical Professor of Medicine. He was Associate Attending Physician at the Presbyterian Hospital, Chicago, 1930-46, and Attending Physician at Henrotin Hospital, Grant Hospital and Research and Educational Hospitals from 1946 until his death.

Among the earliest members of the American Diabetes Association, Dr. Thompson also served as president of the Chicago Medical Society, the American Goiter Association, the Mississippi Valley Medical Society, and the American Geriatrics Society. He was a member of the Governing Body of the International Association of Gerontology, the Council of the American Therapeutic Society and the Board of Trustees of the Mississippi Valley Medical Society. He was a fellow of the American College of Physicians, and a member of the Association of American Physicians, The Endocrine Society, and of many other medical societies.

He was editor of the Journal of the American Geriatrics Society and of the Journal of Clinical Endocrinology and Metabolism. Dr. Thompson contributed numerous articles to medical journals and textbooks. His scientific investigations added fundamental knowledge of diseases of metabolism.

His tremendous vigor and untiring efforts contributed greatly to the improvement of the many medical organizations with which he was associated.